DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

**TRANSMITTED BY FACSIMILE**

Mr. Charles Davis
Senior Director, Regulatory Affairs
Maxim Pharmaceuticals, Inc.
8899 University Center Lane, Suite 400
San Diego, CA 92122

**RE: NDA #[ ]**
**Ceplene™ (histamine dihydrochloride) for Injection**
**MACMIS ID# 10042**

Dear Mr. Davis:

On December 27, 2000, the Division of Drug Marketing, Advertising, and Communications (DDMAC) sent an untitled letter to Maxim Pharmaceuticals (Maxim) concerning its promotion of histamine dihydrochloride for injection, an investigational drug, as safe and effective. This was observed by DDMAC at Maxim's exhibit booth during the 35th American Society of Health-System Pharmacists (ASHP) Midyear Clinical Meeting held in Las Vegas on December 4, 2000. In its January 10, 2001, written response to this untitled letter, Maxim stated that it would cease making claims that promote histamine dihydrochloride as safe or effective prior to approval and cease the distribution or use of any promotional materials for histamine dihydrochloride that contain the same or similar violative statements. Based on Maxim's representations, DDMAC considered the matter closed.

Despite Maxim's assurance that it would not promote histamine dihydrochloride as safe or effective prior to approval, DDMAC has become aware that Maxim is continuing to conduct similar promotional activities for histamine dihydrochloride that are in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Specifically, DDMAC observed Maxim promoting histamine dihydrochloride as safe and effective at the 37th American Society of Clinical Oncology (ASCO) Annual Meeting held in San Francisco, California. Similar promotional claims were also found on your website www.maxim.com (5/21/01). As stated in our December 27, 2000, letter to you, regulations do not permit a sponsor, investigator, or any person acting on their behalf to represent–in a promotional context–that an investigational drug is safe or effective for the purpose under investigation.

**Promotional Activities at the 37th ASCO Annual Meeting**

On May 12, 2001, DDMAC observed one of Maxim's employees at your exhibit booth explaining to visitors the following about histamine dihydrochloride:

> *"Phase III studies are showing a doubling of survival. I would love to tell you more but I can't in case your with the FDA."*
>
> *"You can save on costs by using histamine dihydrochloride in combination with [cytokine interleukin 2] IL-2 because you can send patients home earlier and they can inject themselves."*
>
> *"When histamine dihydrochloride is combined with IL-2 in malignant melanoma less IL-2 needs to be used."*
>
> *"You see less side effects of IL-2 when used with histamine dihydrochloride."*
>
> *"Side effects are transient and will pass in an hour or two."*

In addition, this verbal promotion was reinforced by convention panels, on display in the exhibit booth, that provided a graphic representation suggesting histamine dihydrochloride "creates a more favorable environment for the survival of activated NK cells and T cells" and made the following claims:

> *"In addition to extending survival, the potential to maintain the quality of a patient's life during drug treatment is an important goal of combining histamine dihydrochloride with immunotherapy."*
>
> *"The goal of histamine dihydrochoride/IL-2 combination therapy is to enhance the body's ability to scavenge and attack residual leukemic cells."*
>
> *"Histamine Dihydrochloride: Potentiate immunotherapies by reversing immunosupression caused by the production and release of free radicals."*

Furthermore, two promotional pieces entitled "Creating a Natural Advantage" and "Histamine Dihydrochloride Injection: Mechanism of Action," that were handed out at the exhibit booth, contained similar claims that provided additional reinforcement to the above promotional activities. These promotional activities are in violation of the Act and its implementing regulations because they promote an investigational new drug as safe or effective for uses under investigation.

On May 14, 2001, DDMAC contacted Maxim and requested the immediate removal of violative promotional materials from the exhibit area at the 37th ASCO Annual Meeting. Maxim agreed to comply with this request and asked for a teleconference for further clarification of DDMAC's position. This teleconference took place on May 21, 2001.

**Website www.maxim.com**

Maxim makes numerous claims regarding the safety and efficacy of histamine dihydrochloride on its website. These claims are based solely upon preliminary and inconclusive data since the clinical studies of histamine dihydrochloride are in the initial stages of investigation. In addition, on January 18, 2001, Maxim received a letter from the Food and Drug Administration (FDA) stating that its new drug application for histamine dihydrochloride received on July 19, 2000, was not approvable. Therefore, the website is in violation of the Act and its implementing regulations because it promotes an investigational new drug as safe or effective for uses under investigation.

Following are selected statements from the website that promote histamine dihydrochloride as safe or effective (emphasis added):

> *"The Phase 3 trial demonstrated that combination therapy using Ceplene plus the cytokine interleukin-2 (IL-2)* ***showed a significant improvement in the survival*** *of advanced metastatic melanoma patients with liver involvement (p = 0.0040) and* ***did not impair quality of life*** *over treatment with IL-2 alone." (www.maxim.com/melanoma.html)*
>
> *"****In addition to extending survival****, the potential to maintain the quality of a patient's life during treatment is an important goal of combining Ceplene with immunotherapy. Many currently available treatments for cancer and some infectious diseases are as harsh as the illnesses themselves, forcing patients to make the difficult choice of whether to continue therapy." (www.maxim.com/ceplene_oview.html)*
>
> *"Because Ceplene is designed to increase the effectiveness of cytokines, lower doses of cytokines such as IL-2 and IFN- may potentially be used in combination with Ceplene* ***without compromising therapeutic effectiveness, with the goal of reducing side effects and maintaining the patient's quality of life****." (www.maxim.com/ceplene_works.html)*
>
> *"Maxim Reports 72-week Results From Completed Phase 2 Hepatitis C Study* ***Demonstrating Benefit*** *Of Treatment With Ceplene." (www.maxim.com)*
>
> *"Maxim Researchers Present* ***Favorable Renal Cell Data*** *And Other Ceplene Research At ASCO Conference." (www.maxim.com)*

**Conclusion**

In the teleconference of May 21, 2001, DDMAC requested that Maxim and its representatives immediately cease making claims that promote histamine dihydrochloride as safe or effective prior to approval and cease the distribution or use of any promotional materials for histamine dihydrochloride that contain the same or similar violative statements, including its website. In light of Maxim's commitment to do so, we consider this matter closed.

Maxim should direct any questions 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 # 10042 in addition to the NDA number. DDMAC reminds Maxim 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
5/31/01 02:16:03 PM

MAXIM

PHARMACEUTICALS

# Creating a Natural Advantage

## *MAXIM PHARMACEUTICALS RESEARCH AND DEVELOPMENT*

*Maxim is developing a new generation of advanced drugs and therapies for cancer, infectious diseases, topical disorders, and degenerative diseases. Maxim's research pipeline includes three technology platforms; Ceplene, MaxDerm and the caspase modulator technology.*

## *CEPLENE*

*Maxim's investigational drug candidate, Ceplene™ (histamine dihydrochloride) Injection, formerly known as Maxamine®, is being evaluated for its potential to improve the immune system's ability to fight cancer and viral infections by protecting critical immune cells. Ceplene is administered in combination with cytokines, a class of proteins that stimulate these same immune cells. In addition to extending survival, the potential to maintain the quality of a patient's life during treatment is an important goal of combining Ceplene with immunotherapy. Ceplene is being evaluated as a therapy to be self-administered by patients at home.*

*Ceplene is currently being tested in Phase 3 clinical trials in 12 countries for malignant melanoma and acute myelogenous leukemia (AML), and in Phase 2 trials for the treatment of renal cell carcinoma (a cancer of the kidneys) and hepatitis C.*

### CEPLENE FOR CANCER

### Malignant Melanoma

Malignant melanoma is the most deadly form of skin cancer, with approximately 90,000 new cases and 15,000 deaths annually in the United States, Europe and Australia. At present, there is no effective treatment for advanced melanoma.

In March 2000, Maxim completed a 305-patient U.S. Phase 3 trial of *Ceplene* in combination with the cytokine interleukin-2 (IL-2) in advanced metastatic melanoma. A second Phase 3 trial, conducted in Europe, Australia, Canada and Israel, is designed to compare cytokine therapy combined with *Ceplene* to dacarbazine (DTIC), the most commonly used chemotherapeutic agent for advanced malignant melanoma.

The FDA has granted orphan drug status to *Ceplene* for the treatment of advanced malignant melanoma.

### Acute Myelogenous Leukemia (AML)

AML is the most common acute leukemia in adults, with approximately 10,000 new cases and 7,300 deaths annually in the United States. A majority of patients achieve complete remission after chemotherapy; however, 75-80% relapse within a median of 12 months, and less than five percent survive long term. The goal of *Ceplene*/IL-2 combination therapy is to enhance the body's ability to scavenge and attack residual leukemic cells.

Maxim is conducting a Phase 3 AML clinical trial based in 12 countries, to investigate whether *Ceplene* can prolong leukemia-free remission time and prevent patient relapse compared to the current standard of care, which is no therapy during remission.

The FDA has granted orphan drug status to *Ceplene* for the treatment of AML.

### CEPLENE FOR INFECTIOUS DISEASE

### Hepatitis C

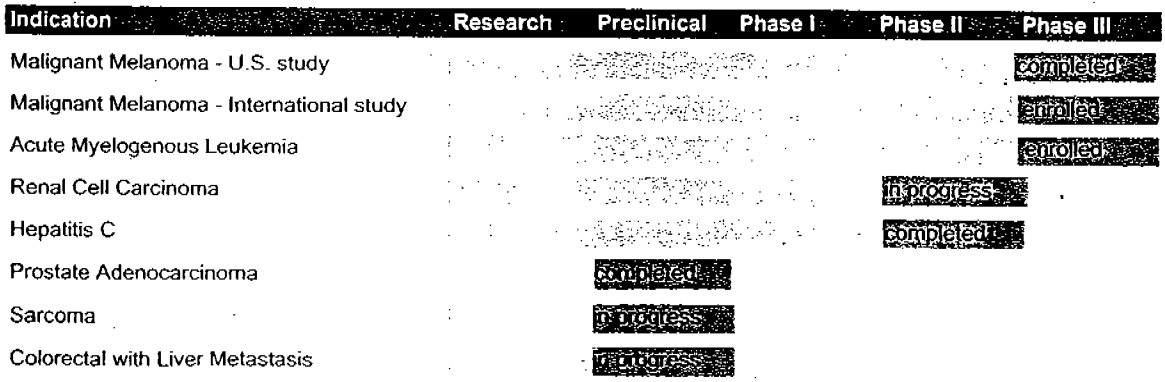
Hepatitis C is more easily transmitted than HIV and is now the leading blood-borne infection in the United States. The U.S. Center for Disease Control and Prevention estimates that over 4.5 million Americans are infected with the hepatitis C virus. The World Health Organization and other sources estimate that more than 200 million people are infected worldwide.

Hepatitis is characterized by inflammation of the liver and, in many cases, permanent cirrhosis (scarring) of the liver and death. The majority of patients do not effectively respond to existing therapies.

Maxim is conducting an international Phase II dose-ranging study of *Ceplene* in combination with interferon-alpha (IFN-α) in previously untreated, chronically infected hepatitis C patients. This study will evaluate the most appropriate dosing regimen for *Ceplene*, and whether *Ceplene* may benefit patients receiving IFN-α in hepatitis C treatment.

*-continued on back*

### Ceplene Current Ongoing Clinical Trial Status




**U.S. Phase 3 clinical study was completed in 2000. At the December 13, 2000 ODAC meeting the FDA indicated that additional data, potentially from additional clinical research focusing on metastatic melanoma patients with liver metastases, will likely be required to support approval.*

*Infectious Disease (continued from front)*

Additionally, Maxim has initiated a clinical study to evaluate the safety of triple-drug therapy incorporating *Ceplene* plus IFN-α and ribavirin in patients with chronic hepatitis C infection who were nonresponsive to prior therapy.

Maxim has entered into a collaboration with Hoffmann - LaRoche for the development of *Ceplene* in combination with the investigational compound Pegasys®, Roche's pegylated interferon-alpha agent (sustained release) in two Phase 3 trials in hepatitis C.

## TOPICAL DISORDERS

### MaxDerm: A Novel Technology

Maxim has developed product candidates based on its *MaxDerm™* technology that allow for topical delivery of histamine dihydrochloride. The novel *MaxDerm* technology is designed to modulate immune, inflammatory and wound healing responses and is being investigated for conditions for which topical therapy is appropriate, including herpes, oral mucositis, shingles, decubitus ulcers and other dermatological ailments.

## CASPASE MODULATORS

### Caspase Program: Expanding the Product Pipeline

Maxim is developing small-molecule inhibitors and activators of caspases, key enzymes that modulate and carry out the cellular signaling pathways involved in programmed cell death, also known as apoptosis. Compounds that inhibit caspases may form the basis for important new drugs for a wide variety of disease targets, such as cardiovascular disease, stroke, and other degenerative diseases. Compounds that induce caspases may serve as new drugs for cancer. A key component of Maxim's research is a proprietary high-throughput screening technology used to identify compounds that either inhibit or activate caspases.

Our research with regard to our caspase modulator drug candidates represents an early stage discovery and development program for which human clinical trials have not yet been initiated.

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**For additional information, visit our website: www.maxim.com**

*This document contains certain forward-looking statements that involve risks and uncertainties. Such forward-looking statements include the efficacy and intended utilization of Ceplene, MaxDerm, caspase modulator compounds, and the Company's clinical trials. Such statements are only predictions and the Company's actual results may differ materially from those anticipated in these forward-looking statements.*




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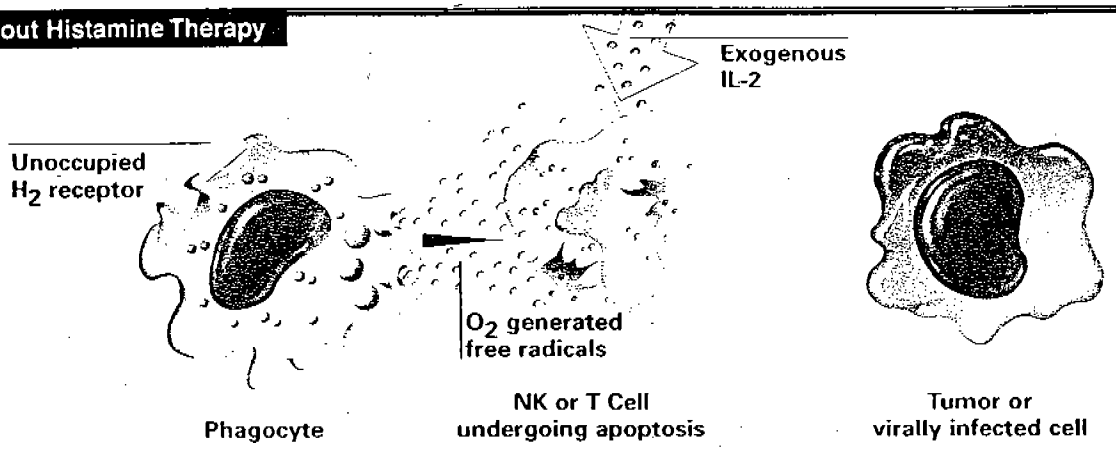
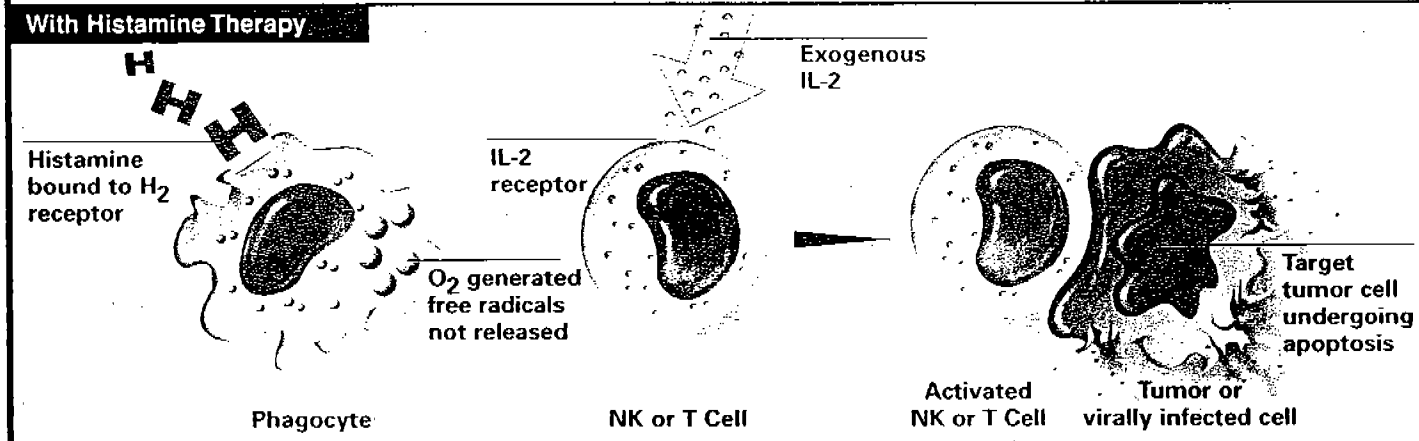
# Histamine Dihydrochloride Injection
# Mechanism of Action

**Without Histamine Therapy**




The activation of NK and T cells by exogenous cytokines is irreversibly blocked by the release of free radicals from phagocytes in tumors and virally infected tissues. These free radicals induce apoptosis in NK and T cells.

**With Histamine Therapy**




Histamine dihydrochloride inhibits the production and release of free radicals (also known as ROS, reactive $O_2$ species), thereby creating a more favorable environment for the survival of activated NK cells and T cells.

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# Extending Life ... with Quality

Maxim is developing a new generation of advanced drugs and therapies for cancer, infectious diseases, topical disorders, and other unmet medical needs. Maxim's goal is to develop and commercialize products that *extend life ... with quality*. The Company's lead drug candidate, *Ceplene*™ (histamine dihydrochloride), is currently being tested in Phase 3 cancer clinical trials in 12 countries for malignant melanoma and acute myelogenous leukemia, and in U.S. Phase 2 trials for the treatment of hepatitis C and renal cell carcinoma.

Please browse our site to learn more about Maxim, our products, and our current clinical trials. Or contact us for additional information.

Upcoming Events

## RECENT NEWS

Maxim Researchers Present Favorable Renal Cell Data And Other Ceplene Research At ASCO Conference

Maxim Reports 72-week Results From Completed Phase 2 Hepatitis C Study Demonstrating Benefit Of Treatment With Ceplene

Maxim Announces That Ceplene™ Will Be Included In Multi-National Study Of Individualized Treatment For Hepatitis C

Maxim Presentations At American Association For Cancer Meeting Highlight Ceplene™ Impact On Immune System

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This report contains forward-looking statements that involve risks and uncertainties. Such forward-looking statements include statements regarding the results of product development efforts and clinical trials, and the scope and success of future operations. Such statements are only predictions and our actual results may differ materially from those anticipated in these forward-looking statements. Factors that may cause such differences include, but are not limited to, those discussed under "Risk Factors" and elsewhere in our filings with the Securities and Exchange Commission, including the uncertainties associated with product development, the risk that products that appeared promising in early clinical trials do not demonstrate efficacy in larger-scale clinical trials, the risk that we will not obtain approval to market our products, the need for additional financing, and the dependence upon collaborative partners.

Note: *Maxamine, Maxamine Therapy, MaxDerm* and the Maxim logo are trademarks of the company.

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# Products & technologies

## Ceplene™ Therapy

### *Ceplene*™ - DESIGNED WITH THE GOAL OF IMPROVING IMMUNOTHERAPY



560,000 deaths from cancer each year in the U.S.

1.2 million new cases of cancer each year in the U.S.

4.5 million people infected with hepatitis C in the U.S.

200 million people infected with hepatitis C worldwide

The need for more effective treatments for many cancers and infectious diseases is well known by patients and their families. *Ceplene*™ (histamine dihydrochloride) was designed with the goal of improving immunotherapy - the use of the immune system to fight cancer and viral infections. More than 800 patients have been treated with *Ceplene* in Maxim's completed and ongoing clinical trials. *Ceplene* is currently being tested in two Phase 3 cancer clinical trials in 12 countries for malignant melanoma and acute myelogenous leukemia (AML), and in U.S. Phase 2 trials for the treatment of renal cell carcinoma, a cancer of the kidneys. *Ceplene* is also under clinical development for the treatment of hepatitis C, a viral infection targeting the liver. Hepatitis C is more easily transmitted than HIV and is now the leading blood-borne infection in the United States.

In addition to extending survival, the potential to maintain the quality of a patient's life during treatment is an important goal of combining *Ceplene* with immunotherapy. Many currently available treatments for cancer and some infectious diseases are as harsh as the illnesses themselves, forcing patients to make the difficult choice of whether to continue therapy. *Ceplene* is being evaluated as a therapy to be self-administered by patients at home.

In many patients with cancer and chronic infectious diseases, the capacity of the patient's immune system to detect and destroy tumor cells or virally infected cells is compromised. Maxim is evaluating the administration of *Ceplene*, an immuno-modulator that protects critical immune cells, with the administration of certain agents that stimulate these immune cells (these agents include cytokines such as interleukin-2 and interferon-alpha, and tumor vaccines). This combination of actions is designed with the goal of improving the immune system's ability to identify, disable and destroy malignant or infected cells.

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# Products & technologies

## Ceplene™ Therapy

## MALIGNANT MELANOMA



### Advanced Malignant Melanoma Overview

Malignant melanoma is the most deadly and serious form of skin cancer and is one of the most rapidly increasing cancers in the world. There are approximately 90,000 new cases of malignant melanoma and 15,000 deaths from the disease each year in the United States, Europe and Australia.

At present, there is no effective treatment for advanced stage IV melanoma. Treatment with chemotherapy, immunotherapy and combination biochemotherapy has provided varying tumor response rates with little or no improvement in survival duration. Advanced-stage melanoma is a large unmet medical need where more effective treatments are required that can improve survival while maintaining patient quality of life.

### *Ceplene*™ (histamine dihydrochloride) U.S. Phase 3 Trial

In March 2000, we completed our 305-patient U.S. Phase 3 trial of *Ceplene* in advanced metastatic melanoma. The Phase 3 trial demonstrated that combination therapy using *Ceplene* plus the cytokine interleukin-2 (IL-2) showed a significant improvement in the survival of advanced metastatic melanoma patients with liver involvement ($p = 0.0040$) and did not impair quality of life over treatment with IL-2 alone.

In July 2000 we submitted our NDA to the FDA seeking approval to market *Ceplene* in the United States as an adjuvant to IL-2 for the treatment of advanced metastatic melanoma with liver metastases. The NDA was granted priority review in September 2000 under accelerated approval statues. In the December 2000 meeting of the Oncologic Drugs Advisory Committee (ODAC), the FDA indicated that additional clinical research will likely be required to support approval, and ODAC declined to recommend approval for metastatic melanoma patients with liver metastases. The Company is committed to pursuing approval of *Ceplene* for this indication, and is in ongoing discussion with the FDA to devise an appropriate strategy to achieve this goal.

A second Phase 3 trial, centered in Europe, Australia, Canada and Israel, is designed to compare cytokine therapy combined with *Ceplene* to dacarbazine (DTIC), the most commonly used chemotherapeutic agent for the treatment of advanced malignant melanoma.

The FDA has granted orphan drug status to *Ceplene* for the treatment of advanced malignant melanoma.

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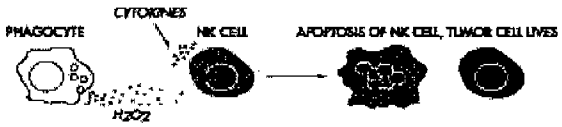
# Products & technologies

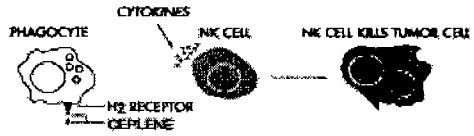
## Ceplene™ Therapy

### HISTAMINE DIHYDROCHLORIDE SHOWN TO PROTECT IMMUNE CELLS - A NOVEL MECHANISM






*Phagocytic cells, which are present in tumors, inhibit the tumoricidal activity of NK-cells and T-cells and can prevent their activation by cytokines such as IL-2 or IFN-α.*




*Maxim researchers have discovered in in vitro experiments that when histamine dihydrochloride (Ceplene) binds to the type-2 histamine receptor (H2 receptor) on the surface of phagocytic cells, it can block the production of Reactive Oxygen Species (ROS) such as hydrogen peroxide ($H_2O_2$), resulting in enhanced activation of NK-cells and T-cells. Histamine's protection of NK and T-cell function may serve as an adjunct to stimulation of these functions by cytokines or other biological response modifiers.*

The scientific foundation for the evaluation of the combination of *Ceplene* plus cytokines or other biological response modifiers is based on discoveries by the Company's scientists at the University of Goteborg, Sweden. *Ceplene* is based on the naturally occurring molecule histamine, which preserves the functions of two kinds of immune cells in *in vitro* experiments, the natural killer-cells (NK-cells) and T-cells, both of which possess an ability to kill and support the killing of cancer cells and virally infected cells.

The killing activity of NK-cells and T-cells can be stimulated by certain agents such as cytokines, naturally occurring proteins. The cytokines IL-2 and IFN-α have been studied and used for the treatment of many cancers and infectious diseases, but results have been largely disappointing in most indications. Maxim's research may explain, in part, why cytokine therapy using IL-2 or IFN-α alone has demonstrated limited efficacy. Phagocytic cells, present in large quantities at the site of malignant cell growth, may inhibit the tumor-killing activity of NK-cells and T-cells by releasing reactive oxygen species (ROS). ROS such as $H_2O_2$ induce self-destruction (apoptosis) of NK-cells and T-cells, preventing the NK-cells and T-cells from attacking the tumor and thus limiting the potential therapeutic effect of cytokines by themselves.

Because *Ceplene* is designed to increase the effectiveness of cytokines, lower doses of cytokines such as IL-2 and IFN-α may potentially be used in combination with *Ceplene* without compromising therapeutic effectiveness, with the goal of reducing side effects and maintaining the patient's quality of life. The Company expects that such combinations may ultimately encompass the addition of *Ceplene* to a broad range of cytokines and other

biological response modifiers (agents designed to stimulate the immune system).

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