Back to the Future:
Original Liquid Leukine® Coming Soon

Bayer Healthcare Pharmaceuticals, with concurrent guidance from the FDA, is reintroducing the previously marketed liquid formulation of its recombinant human granulocyte-macrophage colony-stimulating factor, Leukine® (GM-CSF; sargramostim)—and it does not contain the EDTA (edentate disodium) component. On January 23, 2008, Bayer voluntarily withdrew the product after post-marketing safety reports indicated an upward trend in adverse events, in particular, that of syncope. This increase was determined to be temporally correlated with the recent addition of EDTA to the liquid formulation as Bayer has not observed an upward trend in reporting rates in these adverse events with lyophilized Leukine (a non-EDTA formulation). The decision to withdraw was made in consultation with the United States Food and Drug Administration (FDA).

Identifying the EDTA Problem

Approved by the FDA as a preservative in packaged foods, vitamins, and even baby food, EDTA, a chelating agent, traps metal impurities and thereby extends the shelf life of organic products—making it a logical adjunct to a protein-based therapeutic such as Leukine. However, once added, something about the EDTA/Leukine formulation just didn't add up: "What we saw in our routine safety reporting was an increase in events, and that sparked our concern," says Pamela Cyrus, MD, Vice President US Medical Affairs, Bayer Healthcare.

The uptick in adverse events coincided with the introduction of the EDTA formulation; and a review of the scientific literature provided clues to a possible mechanism. "The addition of EDTA appears to increase the absorption rate of GM-CSF, the active ingredient in Leukine, and may result in a temporary increase in plasma concentration of GM-CSF shortly after administration," says Cyrus. This unanticipated boost to the pharmacodynamic properties of Leukine likely contributed to the transient adverse events observed in some patients.

Bayer's Prompt Response

Once the driver of the adverse events was identified, Bayer's response was both rapid and comprehensive; the EDTA formulation was recalled, and at the same time measures were taken to ensure that patients with the greatest need would continue to receive this critical treatment benefit. "As we withdrew the EDTA-containing formulation we were able to work closely with our supply partners to increase our stock of the lyophilized formulation," says Cyrus. "This enabled us to create and maintain a special access program."

The program was designed to prioritize a reserve of lyophilized Leukine, ensuring a ready source of drug to patients following induction chemotherapy for acute myelogenous leukemia (AML), as well as to those who experience bone marrow transplantation (BMT) failure, or engraftment delay. Leukine is the only myeloid growth factor approved to reduce the incidence of infections resulting in early death following induction chemotherapy in older adults with AML, and to prolong survival of patients with bone marrow graft failure or engraftment delay, as compared to historical experience.

Through the aggressive efforts of Bayer and their manufacturing partners, the special access program avoided shortages that may have seriously impacted patient care. "There's been some disruption in the marketplace, but we are grateful that we've been in a position to assure access for those patients in the greatest need. From the very beginning, in conjunction with the FDA, we pledged that we would ensure that there was sufficient stock for AML and BMT patients. We've been pleased that our lyophilized stock situation has enabled us to continue to provide additional stock into the general market," says Cyrus.

Reintroduction and Reformulation of Leukine

A seemingly minor change in formulation—directly noticed by few consumers—caught the attention of the many once their concerns were voiced. Therefore, to allay those concerns retelling the Leukine success story is in order as this highly-effective hematopoietic growth factor returns to the marketplace.

Originally approved by the FDA in 1991 (with the liquid formulation approved in 1995), Leukine was developed and then marketed by Immunex. Prior to and contingent upon Amgen's acquisition of Immunex, the rights to manufacture Leukine were then sold in July of 2002 to Berlex Laboratories, the US affiliate of Schering AG. In April 2007 Schering/Berlex was acquired by Bayer Healthcare, however, just preceding this transaction, Berlex sought, and gained FDA approval for the EDTA-containing liquid Leukine formulation.

Once aware of this lineage it becomes apparent that the tenure of the EDTA formulation was brief. Less obvious is the fact that the newly available liquid Leukine is the very same formulation proven safe and effective in the original registration trials—a compound that has since gone on to be prescribed for over 200,000 patients.

Safety and Efficacy Results

The pivotal study of the non-EDTA liquid Leukine formulation was conducted by The Eastern Cooperative Oncology Group (E1490; Rowe, et al). In this Phase 3, randomized, double-blind, placebo-controlled trial, treatment-naive patients with AML between the ages of 55 and 70 underwent 10 days of induction therapy with daunorubicin plus cytarabine, followed on day 11 by either Leukine (n = 52) or placebo (n = 47). Study endpoints were: time to hematologic recovery—defined as an absolute neutrophil count (ANC) of greater than 1,500 cells/mm^3—and, incidence of life threatening and severe complications due to infection.

Results of this investigation showed that there was a statistically significant difference in time to ANC recovery >1000/mm^3: 14 days for patients treated with Leukine versus 21 days for placebo (P = .003). This accelerated recovery of the ANC in the Leukine cohort translated into dramatic differences in morbidity and mortality. Leukine-supported patients experienced 75% fewer fatal infections, including 74% fewer deaths among those patients with pneumonia (P = .046), and 83% fewer deaths associated with fungal infections (P = .02). Overall, the median survival for all patients was 10.6 months in the GM-CSF group and 4.8 months in the placebo arm (P = .048).

Conversely, the rate of adverse events in the treatment arm, ranging from mild to moderate, was not significantly different than that observed with placebo. Indeed, in three prospective, randomized trials only one adverse event was significantly increased in patients receiving non-EDTA liquid Leukine, that being skin-associated injection-site reactions. Other transient, low grade events occasionally observed in clinical trials have included fluid retention, dyspnea, supraventricular tachycardia, and laboratory abnormalities such as increases in creatinine, bilirubin, and liver enzymes.

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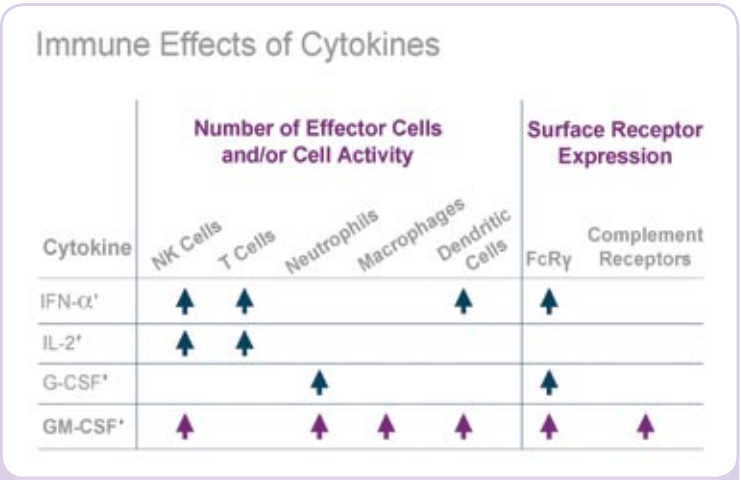
Cytokine Class

Side effects are, in the most general sense, a phenomenon of off-target activity caused by an agent which is not endogenous to the human body. Leukine, or GM-CSF, belongs to a group of regulatory peptides called cytokines which occur naturally in the body. Using recombinant technology, and a suitable host organism, cytokines can be manufactured which are homologous, or nearly so, to the endogenous compound. This particular class of cytokine, a group known as colony stimulating factors (CSFs) affect cells of the hematopoietic system, regulating cell proliferation, differentiation, and enhancement of cell functionality.



Immune Effects of Cytokines

There are three types of CSFs currently marketed: GM-CSF (Leukine), G-CSF, and Peg G-CSF. The latter two agents differ in their pharmacokinetic profile; the former two differ in their range of activity on the myeloid lineage. G-CSF predominantly affects the production of neutrophils, whereas GM-CSF affects not only the production of neutrophils, but Natural Killer (NK) cells which attack tumor cells, or cells infected with virus; macrophages, which capture and digest foreign invaders (and are thought to have greater activity than neutrophils); and dendritic cells, the most potent of the white blood cells which are able to train the various components of the immune system to recognize and respond to antigen.

Providing 24-hour Support

Bayer Healthcare continues to sponsor a free service called the Look to Leukine Program. This initiative provides for 24-hour patient support from oncology nurses via the LEUKLine at 1-877-3LEUKINE, as well as advice regarding reimbursement issues, and educational materials to give the patient a fuller understanding of science behind, and the true benefit of GM-CSF support. Training programs are also available for oncology office professionals. These services, including the advice of nurse advocates, or any question regarding the non-EDTA liquid Leukine formulation, can be obtained through the product website, Leukine.com, or by calling 1-888-84-BAYER.

1. Chen et al. *Eur J Immunol.* 1986;16:767-770. (T lymphocytes); Fultz and Vogel. *J Leukoc Biol.* 1992;51:300-304. (FcR); Luft et al. *J Immunol.* 1998;161:1947-1953. (dendritic cells); Nielsen et al. *Leuk Res.* 1989;13:451-456. (NK cells)
2. Chun and Hoffmann. *Lymphokine Res.* 1982;1:91-98. (NK cells); Watson and Mochizuki. *Immunol Rev.* 1980;51:257-278. (T cells)
3. Buckle and Hogg. *J Immunol.* 1989;143:2295-2301. (FcR); Lopez et al. *J Immunol.* 1983;131:2983-2988. (neutrophils)
4. Grabstein et al. *Science.* 1986;232:506-508. (macrophages); Masucci et al. *Cancer Immunol Immunother.* 1989;29:288-292.; Socinski et al. *Blood.* 1988;72:691-697. (FcR); Steis et al. *J Natl Cancer Inst.* 1990;82:697-703.; Witmer-Pack et al. *J Exp Med.* 1987;166:1484-1498. (dendritic cells); Yuo et al. *Biochem Biophys Res Comm.* 1990;171:491-491. (CR)

Original liquid LEUKINE, not containing EDTA, has been prescribed for more than 200,000 patients over 10 years

LEUKINE is indicated for use following induction chemotherapy in older adults with AML to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death.

Important Information

In controlled clinical trials across all indications, no significant differences were observed between LEUKINE- and placebo-treated patients in the type or frequency of adverse events with the exception of an increase in skin-associated events in the LEUKINE group in the pivotal AML trial. There were occasional reports of fluid retention, dyspnea, supraventricular tachycardia, and laboratory abnormalities (increases in creatinine, bilirubin, and liver enzymes). Other adverse events have been reported; please see accompanying full Prescribing Information, which contains a more complete listing of indications, contraindications, warnings, precautions, adverse reactions, and dosage and administration guidelines.

Please see brief summary of Prescribing Information on adjacent page.

Leukine®
sargramostim
A Recombinant GM-CSF–Yeast-Expressed
Get More From Your CSF

Bayer HealthCare Pharmaceuticals

Leukine®
sargramostim

A Recombinant GM-CSF–Yeast-Expressed

Rx only

The following is a brief summary. Before prescribing, please consult full package insert.

INDICATIONS AND USAGE

Use Following Induction Chemotherapy in Acute Myelogenous Leukemia LEUKINE is indicated for use following induction chemotherapy in older adult patients with acute myelogenous leukemia (AML) to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death. The safety and efficacy of LEUKINE have not been assessed in patients with AML under 55 years of age.

The term acute myelogenous leukemia, also referred to as acute non-lymphocytic leukemia (ANLL), encompasses a heterogeneous group of leukemias arising from various non-lymphoid cell lines which have been defined morphologically by the French-American-British (FAB) system of classification.

Use in Mobilization and Following Transplantation of Autologous Peripheral Blood Progentior Cells LEUKINE is indicated for the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis. Mobilization allows for the collection of increased numbers of progenitor cells capable of engraftment as compared with collection without mobilization. After myeloablative chemotherapy, the transplantation of an increased number of progenitor cells can lead to more rapid engraftment, which may result in a decreased need for supportive care. Myeloid reconstitution is further accelerated by administration of LEUKINE following peripheral blood progenitor cell transplantation.

Use in Myeloid Reconstitution After Autologous Bone Marrow Transplantation LEUKINE is indicated for acceleration of myeloid recovery in patients with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) and Hodgkin's disease undergoing autologous bone marrow transplantation (BMT). After autologous BMT in patients with NHL, ALL, or Hodgkin's disease, LEUKINE has been found to be safe and effective in accelerating myeloid engraftment, decreasing median duration of antibiotic administration, reducing the median duration of infectious episodes and shortening the median duration of hospitalization. Hematologic response to LEUKINE can be detected by complete blood count (CBC) with differential cell counts performed twice per week.

Use in Myeloid Reconstitution After Allogeneic Bone Marrow Transplantation LEUKINE is indicated for acceleration of myeloid recovery in patients undergoing allogeneic BMT from HLA-matched related donors. LEUKINE has been found to be safe and effective in accelerating myeloid engraftment, reducing the incidence of bacteremia and other culture positive infections, and shortening the median duration of hospitalization.

Use in Bone Marrow Transplantation Failure or Engraftment Delay LEUKINE is indicated in patients who have undergone allogeneic or autologous bone marrow transplantation (BMT) in whom engraftment is delayed or has failed. LEUKINE has been found to be safe and effective in prolonging survival of patients who are experiencing graft failure or engraftment delay, in the presence or absence of infection, following autologous or allogeneic BMT. Survival benefit may be relatively greater in those patients who demonstrate one or more of the following characteristics: autologous BMT failure or engraftment delay, no previous total body irradiation, malignancy other than leukemia or a multiple organ failure (MOF) score $\leq$ two (see CLINICAL EXPERIENCE). Hematologic response to LEUKINE can be detected by complete blood count (CBC) with differential performed twice per week.

CONTRAINDICATIONS

LEUKINE is contraindicated:

1) in patients with excessive leukemic myeloid blasts in the bone marrow or peripheral blood ($\geq$ 10%);
2) in patients with known hypersensitivity to GM-CSF, yeast-derived products or any component of the product;
3) for concomitant use with chemotherapy and radiotherapy.

Due to the potential sensitivity of rapidly dividing hematopoietic progenitor cells, LEUKINE should not be administered simultaneously with cytotoxic chemotherapy or radiotherapy or within 24 hours proceeding or following chemotherapy or radiotherapy. In one controlled study, patients with small cell lung cancer received LEUKINE and concurrent thoracic radiotherapy and chemotherapy or the identical radiotherapy and chemotherapy without LEUKINE. The patients randomized to LEUKINE had significantly higher incidence of adverse events, including higher mortality and a higher incidence of grade 3 and 4 infections and grade 3 and 4 thrombocytopenia.[11]

WARNINGS

Pediatric Use Benzyl alcohol is a constituent of liquid LEUKINE and Bacteriostatic Water for Injection diluent. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. **Liquid solutions containing benzyl alcohol (including liquid LEUKINE) or lyophilized LEUKINE reconstituted with Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol) should not be administered to neonates** (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Fluid Retention Edema, capillary leak syndrome, pleural and/or pericardial effusion have been reported in patients after LEUKINE administration. In 156 patients enrolled in placebo-controlled studies using LEUKINE at a dose of 250 mcg/m^2/day by 2-hour IV infusion, the reported incidences of fluid retention (LEUKINE vs. placebo) were as follows: peripheral edema, 11% vs. 7%; pleural effusion, 1% vs. 0%; and pericardial effusion, 4% vs. 1%. Capillary leak syndrome was not observed in this limited number of studies; based on other uncontrolled studies and reports from users of marketed LEUKINE, the incidence is estimated to be less than 1%. In patients with preexisting pleural and pericardial effusions, administration of LEUKINE may aggravate fluid retention; however, fluid retention associated with or worsened by LEUKINE has been reversible after interruption or dose reduction of LEUKINE with or without diuretic therapy. LEUKINE should be used with caution in patients with preexisting fluid retention, pulmonary infiltrates or congestive heart failure.

Respiratory Symptoms Sequestration of granulocytes in the pulmonary circulation has been documented following LEUKINE infusion[12] and dyspnea has been reported occasionally in patients treated with LEUKINE. Special attention should be given to respiratory symptoms during or immediately following LEUKINE infusion, especially in patients with preexisting lung disease. In patients displaying dyspnea during LEUKINE administration, the rate of infusion should be reduced by half. If respiratory symptoms worsen despite infusion rate reduction, the infusion should be discontinued. Subsequent IV infusions may be administered following the standard dose schedule with careful monitoring. LEUKINE should be administered with caution in patients with hypoxia.

Cardiovascular Symptoms Occasional transient supraventricular arrhythmia has been reported in uncontrolled studies during LEUKINE administration, particularly in patients with a previous history of cardiac arrhythmia. However, these arrhythmias have been reversible after discontinuation of LEUKINE. LEUKINE should be used with caution in patients with preexisting cardiac disease.

Renal and Hepatic Dysfunction In some patients with preexisting renal or hepatic dysfunction enrolled in uncontrolled clinical trials, administration of LEUKINE has induced elevation of serum creatinine or bilirubin and hepatic enzymes. Dose reduction or interruption of LEUKINE administration has resulted in a decrease to pretreatment values. However, in controlled clinical trials the incidences of renal and hepatic dysfunction were comparable between LEUKINE (250 mcg/m^2/day by 2-hour IV infusion) and placebo-treated patients. Monitoring of renal and hepatic function in patients displaying renal or hepatic dysfunction prior to initiation of treatment is recommended at least every other week during LEUKINE administration.

PRECAUTIONS

General Parenteral administration of recombinant proteins should be attended by appropriate precautions in case an allergic or untoward reaction occurs. Serious allergic or anaphylactic reactions have been reported. If any serious allergic or anaphylactic reaction occurs, LEUKINE therapy should immediately be discontinued and appropriate therapy initiated.

A syndrome characterized by respiratory distress, hypoxia, flushing, hypotension, syncope, and/or tachycardia has been reported following the first administration of LEUKINE in a particular cycle. These signs have resolved with symptomatic treatment and usually do not recur with subsequent doses in the same cycle of treatment.

Stimulation of marrow precursors with LEUKINE may result in a rapid rise in white blood cell (WBC) count. If the ANC exceeds 20,000 cells/mm^3 or if the platelet count exceeds 500,000/mm^3, LEUKINE administration should be interrupted or the dose reduced by half. The decision to reduce the dose or interrupt treatment should be based on the clinical condition of the patient. Excessive blood counts have returned to normal or baseline levels within three to seven days following cessation of LEUKINE therapy. Twice weekly monitoring of CBC with differential (including examination for the presence of blast cells) should be performed to preclude development of excessive counts.

Growth Factor Potential LEUKINE is a growth factor that primarily stimulates normal myeloid precursors. However, the possibility that LEUKINE can act as a growth factor for any tumor type, particularly myeloid malignancies, cannot be excluded. Because of the possibility of tumor growth potentiation, precaution should be exercised when using this drug in any malignancy with myeloid characteristics.

Should disease progression be detected during LEUKINE treatment, LEUKINE therapy should be discontinued.

LEUKINE has been administered to patients with myelodysplastic syndromes (MDS) in uncontrolled studies without evidence of increased relapse rates.[13, 14, 15] Controlled studies have not been performed in patients with MDS.

Use in Patients Receiving Purged Bone Marrow LEUKINE is effective in accelerating myeloid recovery in patients receiving bone marrow purged by anti-B lymphocyte monoclonal antibodies. Data obtained from uncontrolled studies suggest that if *in vitro* marrow purging with chemical agents causes a significant decrease in the number of responsive hematopoietic progenitors, the patient may not respond to LEUKINE. When the bone marrow purging process preserves a sufficient number of progenitors (>1.2 x 10^4/kg), a beneficial effect of LEUKINE on myeloid engraftment has been reported.[16]

Use in Patients Previously Exposed to Intensive Chemotherapy/Radiotherapy In patients who before autologous BMT, have received extensive radiotherapy to hematopoietic sites for the treatment of primary disease in the abdomen or chest, or have been exposed to multiple myelotoxic agents (alkylating agents, anthracycline antibiotics and antimetabolites), the effect of LEUKINE on myeloid reconstitution may be limited.

Use in Patients with Malignancy Undergoing LEUKINE-Mobilized PBPC Collection When using LEUKINE to mobilize PBPC, the limited *in vitro* data suggest that tumor cells may be released and reinfused into the patient in the leukapheresis product. The effect of reinfusion of tumor cells has not been well studied and the data are inconclusive.

Information for Patients LEUKINE should be used under the guidance and supervision of a health care professional. However, when the physician determines that LEUKINE may be used outside of the hospital or office setting, persons who will be administering LEUKINE should be instructed as to the proper dose, and the method of reconstituting and administering LEUKINE (see **DOSAGE AND ADMINISTRATION**). If home use is prescribed, patients should be instructed in the importance of proper disposal and cautioned against the reuse of needles, syringes, drug product, and diluent. A puncture resistant container should be used by the patient of the disposal of used needles.

Patients should be informed of the serious and most common adverse reactions associated with LEUKINE administration (see **ADVERSE REACTIONS**). Female patients of childbearing potential should be advised of the possible risks to the fetus of LEUKINE (see **PRECAUTIONS, Pregnancy Category C**).

Laboratory Monitoring LEUKINE can induce variable increases in WBC and/or platelet counts. In order to avoid potential complications of excessive leukocytosis (WBC >50,000 cells/mm^3; ANC >20,000 cells/mm^3), a CBC is recommended twice per week during LEUKINE therapy. Monitoring of renal and hepatic function in patients displaying renal or hepatic dysfunction prior to initiation of treatment is recommended at least biweekly during LEUKINE administration. Body weight and hydration status should be carefully monitored during LEUKINE administration.

Drug Interaction Interactions between LEUKINE and other drugs have not been fully evaluated. Drugs which may potentiate the myeloproliferative effects of LEUKINE, such as lithium and corticosteroids, should be used with caution.

Carcinogenesis, Mutagenesis, Impairment of Fertility Animal studies have not been conducted with LEUKINE to evaluate the carcinogenic potential or the effect on fertility.

Pregnancy (Category C) Animal reproduction studies have not been conducted with LEUKINE. It is not known whether LEUKINE can cause fetal harm when administered to a pregnant woman or can affect reproductive capability. LEUKINE should be given to a pregnant woman only if clearly needed.

Nursing Mothers It is not known whether LEUKINE is excreted in human milk. Because many drugs are excreted in human milk, LEUKINE should be administered to a nursing woman only if clearly needed.

Pediatric Use Safety and effectiveness in pediatric patients have not been established; however, available safety data indicate that LEUKINE does not exhibit any greater toxicity in pediatric patients than in adults. A total of 124 pediatric subjects between the ages of 4 months and 18 years have been treated with LEUKINE in clinical trials at doses ranging from 60-1,000 mcg/m^2/day intravenously and 4-1,500 mcg/m^2/day subcutaneously. In 53 pediatric patients enrolled in controlled studies at a dose of 250 mcg/m^2/day by 2-hour IV infusion, the type and frequency of adverse events were comparable to those reported for the adult population. **Liquid solutions containing benzyl alcohol (including liquid LEUKINE) or lyophilized LEUKINE reconstituted with Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol) should not be administered to neonates** (see **WARNINGS**).

Geriatric Use In the clinical trials, experience in older patients (age $\geq$65 years), was limited to the acute myelogenous leukemia (AML) study. Of the 52 patients treated with LEUKINE in this randomized study, 22 patients were age 65-70 years and 30 patients were age 55-64 years. The number of placebo patients in each age group were 13 and 33 patients respectively. This was not an adequate database from which determination of differences in efficacy endpoints or safety assessments could be reliably made and this clinical study was not designed to evaluate difference between these two age groups. Analyses of general trends in safety and efficacy were undertaken and demonstrate similar patterns for older (65-70 yrs) vs younger patients (55-64 yrs). Greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Autologous and Allogeneic Bone Marrow Transplantation LEUKINE is generally well tolerated. In three placebo-controlled studies enrolling a total of 156 patients after autologous BMT or peripheral blood progenitor cell transplantation, events reported in at least 10% of patients who received IV LEUKINE or placebo were as reported at right:

No significant differences were observed between LEUKINE and placebo-treated patients in the type or frequency of laboratory abnormalities, including renal and hepatic parameters. In some patients with preexisting renal or hepatic dysfunction enrolled in uncontrolled clinical trials, administration of LEUKINE has induced elevation of serum creatinine or bilirubin and hepatic enzymes (see **WARNINGS**). In addition, there was no significant difference in relapse rate and 24 month survival between the LEUKINE and placebo-treated patients.

In the placebo-controlled trial of 109 patients after allogeneic BMT, events reported in at least 10% of patients who received IV LEUKINE or placebo were as reported at right:

There were no significant differences in the incidence or severity of GVHD, relapse rates and survival between the LEUKINE and placebo-treated patients.

Adverse events observed for the patients treated with LEUKINE in the historically-controlled BMT failure study were similar to those reported in the placebo-controlled studies. In addition, headache (26%), pericardial effusion (25%), arthralgia (21%) and myalgia (18%) were also reported in patients treated with LEUKINE in the graft failure study.

In uncontrolled Phase I/II studies with LEUKINE in 215 patients, the most frequent adverse events were fever, asthenia, headache, bone pain, chills and myalgia. These systemic events were generally mild or moderate and were usually prevented or reversed by the administration of analgesics and antipyretics such as acetaminophen. In these uncontrolled trials, other infrequent events reported were dyspnea, peripheral edema, and rash.

Reports of events occurring with marketed LEUKINE include arrhythmia, fainting, eosinophilia, dizziness, hypotension, injection site reactions, pain (including abdominal, back, chest, and joint pain), tachycardia, thrombosis, and transient liver function abnormalities.

In patients with preexisting edema, capillary leak syndrome, pleural and/or pericardial effusion, administration of LEUKINE may aggravate fluid retention (see **WARNINGS**). Body weight and hydration status should be carefully monitored during LEUKINE administration.

Adverse events observed in pediatric patients in controlled studies were comparable to those observed in adult patients.

Acute Myelogenous Leukemia Adverse events reported in at least 10% of patients who received LEUKINE or placebo were as reported at right:

Nearly all patients reported leukopenia, thrombocytopenia and anemia. The frequency and type of adverse events observed following induction were similar between LEUKINE and placebo groups. The only significant difference in the rates of these adverse events was an increase in skin associated events in the LEUKINE group (p=0.002). No significant differences were observed in laboratory results, renal or hepatic toxicity. No significant differences were observed between the LEUKINE and placebo-treated patients for adverse events following consolidation. There was no significant difference in response rate or relapse rate.

In a historically-controlled study of 86 patients with acute myelogenous leukemia (AML), the LEUKINE treated group exhibited an increased incidence of weight gain (p=0.007), low serum proteins and prolonged prothrombin time (p=0.02) when compared to the control group. Two LEUKINE treated patients had progressive increase in circulating monocytes and promonocytes and blasts in the marrow which reversed when LEUKINE was discontinued. The historical control group exhibited an increased incidence of cardiac events (p=0.018), liver function abnormalities (p=0.008), and neurocortical hemorrhagic events (p=0.025).[15]

Antibody Formation Serum samples collected before and after LEUKINE treatment from 214 patients with a variety of underlying diseases have been examined for immunogenicity based on the presence of antibodies. Neutralizing antibodies were detected in five of 214 patients (2.3%) after receiving LEUKINE by continuous IV infusion (three patients) or subcutaneous injection (SC)(two patients) for 28 to 84 days in multiple courses. All five patients had impaired hematopoiesis before the administration of LEUKINE and consequently the effect of the development of anti-GM-CSF antibodies on normal hematopoiesis could not be assessed. Antibody studies of 75 patients with Crohn's disease receiving LEUKINE by subcutaneous injection with normal hematopoiesis and no other immunosuppressive drugs showed one patient (1.3%) with detectable neutralizing antibodies. The clinical relevance of the presence of these antibodies are unknown. Drug-induced neutropenia, neutralization of endogenous GM-CSF activity and diminution of the therapeutic effect of LEUKINE secondary to formation of neutralizing antibody remain a theoretical possibility. Serious allergic and anaphylactoid reactions have been reported with LEUKINE but the rate of occurence of antibodies in such patients has not been assessed.

Overdosage The maximum amount of LEUKINE that can be safely administered in single or multiple doses has not been determined. Doses up to 100 mcg/kg/day (4,000 mcg/m^2/day or 16 times the recommended dose) were administered to four patients in a Phase I uncontrolled clinical study by continuous IV infusion for 7 to 18 days. Increases in WBC up to 200,000 cells/mm^3 were observed. Adverse events reported were dyspnea, malaise, nausea, fever, rash, sinus tachycardia, headache and chills. All these events were reversible after discontinuation of LEUKINE.

In case of overdosage, LEUKINE therapy should be discontinued and the patient carefully monitored for WBC increase and respiratory symptoms.

Percent of AuBMT Patients Reporting Events

Events by Body System	LEUKINE (n=79)	Placebo (n=77)	Events by Body System	LEUKINE (n=79)	Placebo (n=77)
Body, General			**Metabolic, Nutritional Disorder**		
Fever	95	96	Edema	34	35
Mucous membrane disorder	75	78	Peripheral edema	11	7
Asthenia	66	51	**Respiratory System**		
Malaise	57	51	Dyspnea	28	31
Sepsis	11	14	Lung disorder	20	23
Digestive System			**Hemic and Lymphatic System**		
Nausea	90	96	Blood dyscrasia	25	27
Diarrhea	89	82	**Cardiovascular System**		
Vomiting	85	90	Hemorrhage	23	30
Anorexia	54	58	**Urogenital System**		
GI disorder	37	47	Urinary tract disorder	14	13
GI hemorrhage	27	33	Kidney function abnormal	8	10
Stomatitis	24	29	**Nervous System**		
Liver damage	13	14	CNS disorder	11	16
Skin and Appendages					
Alopecia	73	74			
Rash	44	38			

Percent of Allogeneic BMT Patients Reporting Events

Events by Body System	LEUKINE (n=53)	Placebo (n=56)	Events by Body System	LEUKINE (n=53)	Placebo (n=56)
Body, General			**Metabolic/Nutritional Disorders**		
Fever	77	80	Bilirubinemia	30	27
Abdominal pain	38	23	Hyperglycemia	25	23
Headache	36	36	Peripheral edema	15	21
Chills	25	20	Increased creatinine	15	14
Pain	17	36	Hypomagnesemia	15	9
Asthenia	17	20	Increased SGPT	13	16
Chest pain	15	9	Edema	13	11
Back pain	9	18	Increased alk. phosphatase	8	14
Digestive System			**Respiratory System**		
Diarrhea	81	66	Pharyngitis	23	13
Nausea	70	66	Epistaxis	17	16
Vomiting	70	57	Dyspnea	15	14
Stomatitis	62	63	Rhinitis	11	14
Anorexia	51	57	**Hemic and Lymphatic System**		
Dyspepsia	17	20	Thrombocytopenia	19	34
Hematemesis	13	7	Leukopenia	17	29
Dysphagia	11	7	Petechia	6	11
GI hemorrhage	11	5	Agranulocytosis	6	11
Constipation	8	11	**Urogenital System**		
Skin and Appendages			Hematuria	9	21
Rash	70	73	**Nervous System**		
Alopecia	45	45	Paresthesia	11	13
Pruritis	23	13	Insomnia	11	9
Musculo-skeletal System			Anxiety	11	2
Bone pain	21	5	**Laboratory Abnormalities***		
Arthralgia	11	4	High glucose	41	49
Special Senses			Low albumin	27	36
Eye hemorrhage	11	0	High BUN	23	17
Cardiovascular System			Low calcium	2	7
Hypertension	34	32	High cholesterol	17	8
Tachycardia	11	9			

*Grade 3 and 4 laboratory abnormalities only. Denominators may vary due to missing laboratory measurements.

Percent of AML Patients Reporting Events

Events by Body System	LEUKINE (n=52)	Placebo (n=47)	Events by Body System	LEUKINE (n=52)	Placebo (n=47)
Body, General			**Metabolic/Nutritional Disorder**		
Fever (no infection)	81	74	Metabolic	58	49
Infection	65	68	Edema	25	23
Weight loss	37	28	**Respiratory System**		
Weight gain	8	21	Pulmonary	48	64
Chills	19	26	**Hemic and Lymphatic System**		
Allergy	12	15	Coagulation	19	21
Sweats	6	13	**Cardiovascular System**		
Digestive System			Hemorrhage	29	43
Nausea	58	55	Hypertension	25	32
Liver	77	83	Cardiac	23	32
Diarrhea	52	53	Hypotension	13	26
Vomiting	46	34	**Urogenital System**		
Stomatitis	42	43	GU	50	57
Anorexia	13	11	**Nervous System**		
Abdominal distention	4	13	Neuro-clinical	42	53
Skin and Appendages			Neuro-motor	25	26
Skin	77	45	Neuro-psych	15	26
Alopecia	37	51	Neuro-sensory	6	11

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HOW SUPPLIED

Liquid LEUKINE is available in vials containing 500 mcg/mL (2.8 x 10^6 IU/mL) sargramostim. Lyophilized LEUKINE is available in vials containing 250 mcg (1.4 x 10^6 IU/vial) sargramostim.

Each dosage form is supplied as follows: Carton of one multiple use vial; each vial contains 1 mL of preserved 500 mcg/mL liquid LEUKINE (NDC 50419-595-01); Carton of five vials of lyophilized LEUKINE 250 mcg (NDC 50419-002-33); Carton of five multiple use vials; each vial contains 1 mL of preserved 500 mcg/mL liquid LEUKINE (NDC 50419-595-05).

Please see the full Prescribing Information for additional information, including dosage and administration guidelines.

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