Leukine® (sargramostim) **Rx Only**

A Recombinant GM-CSF—Yeast-Expressed

DESCRIPTION

LEUKINE® (sargramostim) is a recombinant human granulocyte-macrophage colony stimulating factor (rhu GM-CSF) produced by recombinant DNA technology in a yeast (*S. cerevisiae*) expression system. GM-CSF is a hematopoietic growth factor which stimulates proliferation and differentiation of hematopoietic progenitor cells. LEUKINE is a glycoprotein of 127 amino acids characterized by three primary molecular species having molecular masses of 19,500, 16,800 and 15,500 daltons. The amino acid sequence of LEUKINE differs from the natural human GM-CSF by a substitution of leucine at position 23, and the carbohydrate moiety may be different from the native protein. Sargramostim has been selected as the proper name for yeast-derived rhu GM-CSF.

The liquid LEUKINE presentation is formulated as a sterile, preserved (1.1% benzyl alcohol), injectable solution (500 mcg/mL) in a vial. Lyophilized LEUKINE is a sterile, white, preservative-free powder (250 mcg) that requires reconstitution with 1 mL Sterile Water for Injection, USP or 1 mL Bacteriostatic Water for Injection, USP. Liquid LEUKINE has a pH range of 6.7 – 7.7 and lyophilized LEUKINE has a pH range of 7.1 – 7.7.

Liquid LEUKINE and reconstituted lyophilized LEUKINE are clear, colorless liquids suitable for subcutaneous injection (SC) or intravenous infusion (IV). Liquid LEUKINE contains 500 mcg (2.8×10^6 IU/mL) sargramostim and 1.1% benzyl alcohol in a 1 mL solution. The vial of lyophilized LEUKINE contains 250 mcg (1.4×10^6 IU/vial) sargramostim. The liquid LEUKINE vial and reconstituted lyophilized LEUKINE vial also contain 40 mg/mL mannitol, USP; 10 mg/mL sucrose, NF; and 1.2 mg/mL tromethamine, USP, as excipients. Biological potency is expressed in International Units (IU) as tested against the WHO First International Reference Standard. The specific activity of LEUKINE is approximately 5.6×10^6 IU/mg.

CLINICAL PHARMACOLOGY

General

GM-CSF belongs to a group of growth factors termed colony stimulating factors which support survival, clonal expansion, and differentiation of hematopoietic progenitor cells. GM-CSF induces partially committed progenitor cells to divide and differentiate in the granulocyte-macrophage pathways which include neutrophils, monocytes/macrophages and myeloid-derived dendritic cells.

GM-CSF is also capable of activating mature granulocytes and macrophages. GM-CSF is a multilineage factor and, in addition to dose-dependent effects on the myelomonocytic lineage, can promote the proliferation of megakaryocytic and erythroid progenitors.[1] However, other factors are required to induce complete maturation in these two lineages. The various cellular responses (i.e., division, maturation, activation) are induced through GM-CSF binding to specific receptors expressed on the cell surface of target cells.[2]

In vitro Studies of LEUKINE in Human Cells

The biological activity of GM-CSF is species-specific. Consequently, *in vitro* studies have been performed on human cells to characterize the pharmacological activity of LEUKINE. *In vitro* exposure of human bone marrow cells to LEUKINE at concentrations ranging from 1–100 ng/mL results in the proliferation of hematopoietic progenitors and in the formation of pure granulocyte, pure macrophage and mixed granulocytemacrophage colonies.[3] Chemotactic, anti-fungal and anti-parasitic[4] activities of granulocytes and monocytes are increased by exposure to LEUKINE *in vitro*. LEUKINE increases the cytotoxicity of monocytes toward certain neoplastic cell lines[3] and activates polymorphonuclear neutrophils to inhibit the growth of tumor cells.

In vivo Primate Studies of LEUKINE

Pharmacology/toxicology studies of LEUKINE were performed in cynomolgus monkeys. An acute toxicity study revealed an absence of treatment-related toxicity following a single IV bolus injection at a dose of 300 mcg/kg. Two subacute studies were performed using IV injection (maximum dose 200 mcg/kg/day x 14 days) and subcutaneous injection (SC) (maximum dose 200 mcg/kg/day x 28 days). No major visceral organ toxicity was documented. Notable histopathology findings included increased cellularity in hematologic organs and heart and lung tissues. A dose-dependent increase in leukocyte count, which consisted primarily of segmented neutrophils, occurred during the dosing period; increases in monocytes, basophils, eosinophils and lymphocytes were also noted. Leukocyte counts decreased to pretreatment values over a 1–2 week recovery period.

Pharmacokinetics

Pharmacokinetic profiles have been analyzed in controlled studies of 24 normal male volunteers. Liquid and lyophilized LEUKINE, at the recommended dose of 250 mcg/m^2, have been determined to be bioequivalent based on the statistical evaluation of AUC.[5]

When LEUKINE (either liquid or lyophilized) was administered IV over two hours to normal volunteers, the mean beta half-life was approximately 60 minutes. Peak concentrations of GM-CSF were observed in blood samples obtained during or immediately after completion of LEUKINE infusion. For liquid LEUKINE, the mean maximum concentration (Cmax) was 5.0 ng/mL, the mean clearance rate was approximately 420 mL/min/m^2 and the mean AUC (0–inf) was 640 ng/mL•min. Corresponding results for lyophilized LEUKINE in the same subjects were mean Cmax of 5.4 ng/mL, mean clearance rate of 431 mL/min/m^2, and mean AUC (0–inf) of 677 ng/mL•min. GM-CSF was last detected in blood samples obtained at three or six hours.

When LEUKINE (either liquid or lyophilized) was administered SC to normal volunteers, GM-CSF was detected in the serum at 15 minutes, the first sample point. The mean beta half-life was approximately 162 minutes. Peak levels occurred at one to three hours post injection, and LEUKINE remained detectable for up to six hours after injection. The mean Cmax was 1.5 ng/mL. For liquid LEUKINE, the mean clearance was 549 mL/min/m^2 and the mean AUC (0–inf) was 549 ng/mL•min. For lyophilized LEUKINE, the mean clearance was 529 mL/min/m^2 and the mean AUC (0–inf) was 501 ng/mL•min.

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 ≤ two (see **CLINICAL EXPERIENCE**). Hematologic response to LEUKINE can be detected by complete blood count (CBC) with differential performed twice per week.

CLINICAL EXPERIENCE

Acute Myelogenous Leukemia

The safety and efficacy of LEUKINE in patients with AML who are younger than 55 years of age have not been determined. Based on Phase II data suggesting the best therapeutic effects could be achieved in patients at highest risk for severe infections and mortality while neutropenic, the Phase III clinical trial was conducted in older patients. The safety and efficacy of LEUKINE in the treatment of AML were evaluated in a multi-center, randomized, double-blind placebo-controlled trial of 99 newly diagnosed adult patients, 55–70 years of age, receiving induction with or without consolidation.[6] A combination of standard doses of daunorubicin (days 1–3) and ara-C (days 1–7) was administered during induction and high dose ara-C was administered days 1–6 as a single course of consolidation, if given. Bone marrow evaluation was performed on day 10 following induction chemotherapy. If hypoplasia with <5% blasts was not achieved, patients immediately received a second cycle of induction chemotherapy. If the bone marrow was hypoplastic with <5% blasts on day 10 or four days following the second cycle of induction chemotherapy, LEUKINE (250 mcg/m^2/day) or placebo was given IV over four hours each day, starting four days after the completion of chemotherapy. Study drug was continued until an ANC ≥1500/mm^3 for three consecutive days was attained or a maximum of 42 days. LEUKINE or placebo was also administered after the single course of consolidation chemotherapy if delivered (ara-C 3–6 weeks after induction following neutrophil recovery). Study drug was discontinued immediately if leukemic regrowth occurred.

LEUKINE significantly shortened the median duration of ANC <500/mm^3 by 4 days and <1000/mm^3 by 7 days following induction (see **Table 1**). 75% of patients receiving LEUKINE achieved ANC >500/mm^3 by day 16, compared to day 25 for patients receiving placebo. The proportion of patients receiving one cycle (70%) or two cycles (30%) of induction was similar in both treatment groups; LEUKINE significantly shortened the median times to neutrophil recovery whether one cycle (12 versus 15 days) or two cycles (14 versus 23 days) of induction chemotherapy was administered. Median times to platelet (>20,000/mm^3) and RBC transfusion independence were not significantly different between treatment groups.

Table 1

Hematological Recovery (in Days): Induction			
Dataset	**sargramostim n=52* Median (25%, 75%)**	**Placebo n=47 Median (25%,75%)**	**p-value†**
ANC>500/mm^3‡	13 (11, 16)	17 (13, 25)	0.009
ANC>1000/mm^3§	14 (12, 18)	21 (13, 34)	0.003
PLT>20,000/mm^3¶	11 (7, 14)	12 (9, >42)	0.10
RBC#	12 (9, 24)	14 (9, 42)	0.53

*Patients with missing data censored.

†p=Generalized Wilcoxon

‡2 patients on sargramostim and 4 patients on placebo had missing values.

§2 patients on sargramostim and 3 patients on placebo had missing values.

¶4 patients on placebo had missing values.

#3 patients on sargramostim and 4 patients on placebo had missing values.

During the consolidation phase of treatment, LEUKINE did not shorten the median time to recovery of ANC to 500/mm^3 (13 days) or 1000/mm^3 (14.5 days) compared to placebo. There were no significant differences in time to platelet and RBC transfusion independence.

The incidence of severe infections and deaths associated with infections was significantly reduced in patients who received LEUKINE. During induction or consolidation, 27 of 52 patients receiving LEUKINE and 35 of 47 patients receiving placebo had at least one grade 3, 4 or 5 infection (p=0.02). Twenty-five patients receiving LEUKINE and 30 patients receiving placebo experienced severe and fatal infections during induction only. There were significantly fewer deaths from infectious causes in

the LEUKINE arm (3 versus 11, p=0.02). The majority of deaths in the placebo group were associated with fungal infections with pneumonia as the primary infection.

Disease outcomes were not adversely affected by the use of LEUKINE. The proportion of patients achieving complete remission (CR) was higher in the LEUKINE group (69% as compared to 55% for the placebo group), but the difference was not significant (p=0.21). There was no significant difference in relapse rates; 12 of 36 patients who received LEUKINE and five of 26 patients who received placebo relapsed within 180 days of documented CR (p=0.26). The overall median survival was 378 days for patients receiving LEUKINE and 268 days for those on placebo (p=0.17). The study was not sized to assess the impact of LEUKINE treatment on response or survival.

Mobilization and Engraftment of PBPC

A retrospective review was conducted of data from patients with cancer undergoing collection of peripheral blood progenitor cells (PBPC) at a single transplant center. Mobilization of PBPC and myeloid reconstitution post-transplant were compared between four groups of patients (n=196) receiving LEUKINE for mobilization and a historical control group who did not receive any mobilization treatment [progenitor cells collected by leukapheresis without mobilization (n=100)]. Sequential cohorts received LEUKINE. The cohorts differed by dose (125 or 250 mcg/m^2/day), route (IV over 24 hours or SC) and use of LEUKINE post-transplant. Leukaphereses were initiated for all mobilization groups after the WBC reached 10,000/mm^3. Leukaphereses continued until both a minimum number of mononucleated cells (MNC) were collected (6.5 or 8.0 x 10^8/kg body weight) and a minimum number of phereses (5–8) were performed. Both minimum requirements varied by treatment cohort and planned conditioning regimen. If subjects failed to reach a WBC of 10,000 cells/mm^3 by day five, another cytokine was substituted for LEUKINE; these subjects were all successfully leukapheresed and transplanted. The most marked mobilization and post-transplant effects were seen in patients administered the higher dose of LEUKINE (250 mcg/m^2) either IV (n=63) or SC (n=41).

PBPCs from patients treated at the 250 mcg/m^2/day dose had significantly higher number of granulocyte-macrophage colony-forming units (CFU-GM) than those collected without mobilization. The mean value after thawing was 11.41 x 10^4 CFU-GM/kg for all LEUKINE-mobilized patients, compared to 0.96 x 10^4/kg for the non-mobilized group. A similar difference was observed in the mean number of erythrocyte burst-forming units (BFU-E) collected (23.96 x 10^4/kg for patients mobilized with 250 mcg/m^2 doses of LEUKINE administered SC vs. 1.63 x 10^4/kg for non-mobilized patients).

After transplantation, mobilized subjects had shorter times to myeloid engraftment and fewer days between transplantation and the last platelet transfusion compared to non-mobilized subjects. Neutrophil recovery (ANC >500/mm^3) was more rapid in patients administered LEUKINE following PBPC transplantation with LEUKINE-mobilized cells (see **Table 2**). Mobilized patients also had fewer days to the last platelet transfusion and last RBC transfusion, and a shorter duration of hospitalization than did non-mobilized subjects.

Table 2

ANC and Platelet Recovery after PBPC Transplant

	Route for Mobilization	Post-transplant LEUKINE	ENGRAFTMENT (median value in days)	
			ANC>500/mm^3	Last platelet transfusion
No Mobilization	—	no	29	28
LEUKINE	IV	no	21	24
250 mcg/m^2	IV	yes	12	19
	SC	yes	12	17

A second retrospective review of data from patients undergoing PBPC at another single transplant center was also conducted. LEUKINE was given SC at 250 mcg/m^2/day once a day (n=10) or twice a day (n=21) until completion of the phereses. Phereses were begun on day 5 of LEUKINE administration and continued until the targeted MNC count of 9 x 10^8/kg or CD34+ cell count of 1 x 10^6/kg was reached. There was no difference in CD34+ cell count in patients receiving LEUKINE once or twice a day. The median time to ANC>500/mm^3 was 12 days and to platelet recovery (>25,000/mm^3) was 23 days.

Survival studies comparing mobilized study patients to the nonmobilized patients and to an autologous historical bone marrow transplant group showed no differences in median survival time.

Autologous Bone Marrow Transplantation[7]

Following a dose-ranging Phase I/II trial in patients undergoing autologous BMT for lymphoid malignancies,[8,9] three single center, randomized, placebo-controlled and double-blinded studies were conducted to evaluate the safety and efficacy of LEUKINE for promoting hematopoietic reconstitution following autologous BMT. A total of 128 patients (65 LEUKINE, 63 placebo) were enrolled in these three studies. The majority of the patients had lymphoid malignancy (87 NHL, 17 ALL), 23 patients had Hodgkin's disease, and one patient had acute myeloblastic leukemia (AML). In 72 patients with NHL or ALL, the bone marrow harvest was purged prior to storage with one of several monoclonal antibodies. No chemical agent was used for *in vitro* treatment of the bone marrow. Preparative regimens in the three studies included cyclophosphamide (total dose 120–150 mg/kg) and total body irradiation (total dose 1,200–1,575 rads). Other regimens used in patients with Hodgkin's disease and NHL without radiotherapy consisted of three or more of the following in combination (expressed as total dose): cytosine arabinoside (400 mg/m^2) and carmustine (300 mg/m^2), cyclophosphamide (140–150 mg/kg), hydroxyurea (4.5 grams/m^2) and etoposide (375–450 mg/m^2).

Compared to placebo, administration of LEUKINE in two studies (n=44 and 47) significantly improved the following hematologic and clinical endpoints: time to neutrophil engraftment, duration of hospitalization and infection experience or antibacterial usage. In the third study (n=37) there was a positive trend toward earlier myeloid engraftment in favor of LEUKINE. This latter study differed from the other two in having enrolled a large number of patients with Hodgkin's disease who had also received extensive radiation and chemotherapy prior to harvest of autologous bone marrow. A subgroup analysis of the data from all three studies revealed that the median time to engraftment for patients with Hodgkin's disease, regardless of treatment, was six days longer when compared to patients with NHL and ALL, but that the overall beneficial LEUKINE treatment effect was the same. In the following combined analysis of the three studies, these two subgroups (NHL and ALL vs. Hodgkin's disease) are presented separately.

Table 3

Autologous BMT: Combined Analysis from Placebo-Controlled Clinical Trials of Responses in Patients with NHL and ALL Median Values (days)

	ANC ≥500/mm^3	ANC ≥1000/mm^3	Duration of Hospitalization	Duration of Infection	Duration of Antibacterial Therapy
LEUKINE (n=54)	18*†	24*†	25*	1*	21*
Placebo (n=50)	24	32	31	4	25

Note: The single AML patient was not included.

*p <0.05 Wilcoxon or CMH ridit chi-squared

†p <0.05 Log rank

Patients with Lymphoid Malignancy (Non-Hodgkin's Lymphoma and Acute Lymphoblastic Leukemia)

Myeloid engraftment (absolute neutrophil count [ANC]≥500 cells/mm^3) in 54 patients receiving LEUKINE was observed 6 days earlier than in 50 patients treated with placebo (see **Table 3**). Accelerated myeloid engraftment was associated with significant clinical benefits. The median duration of hospitalization was six days shorter for the LEUKINE group than for the placebo group. Median duration of infectious episodes (defined as fever and neutropenia; or two positive cultures of the same organism; or fever >38°C and one positive blood culture; or clinical evidence of infection) was three days less in the group treated with LEUKINE. The median duration of antibacterial administration in the post-transplantation period was four days shorter for the patients treated with LEUKINE than for placebo-treated patients. The study was unable to detect a significant difference between the treatment groups in rate of disease relapse 24 months post-transplantation. As a group, leukemic subjects receiving LEUKINE derived less benefit than NHL subjects. However, both the leukemic and NHL groups receiving LEUKINE engrafted earlier than controls.

Patients with Hodgkin's Disease

If patients with Hodgkin's disease are analyzed separately, a trend toward earlier myeloid engraftment is noted. LEUKINE-treated patients engrafted earlier (by five days) than the placebo-treated patients (p=0.189, Wilcoxon) but the number of patients was small (n=22).

Allogeneic Bone Marrow Transplantation

A multi-center, randomized, placebo-controlled, and double-blinded study was conducted to evaluate the safety and efficacy of LEUKINE for promoting hematopoietic reconstitution following allogeneic BMT. A total of 109 patients (53 LEUKINE, 56 placebo) were enrolled in the study. Twenty-three patients (11 LEUKINE, 12 placebo) were 18 years old or younger. Sixty-seven patients had myeloid malignancies (33 AML, 34 CML), 17 had lymphoid malignancies (12 ALL, 5 NHL), three patients had Hodgkin's disease, six had multiple myeloma, nine had myelodysplastic disease, and seven patients had aplastic anemia. In 22 patients at one of the seven study sites, bone marrow harvests were depleted of T cells. Preparative regimens included cyclophosphamide, busulfan, cytosine arabinoside, etoposide, methotrexate, corticosteroids, and asparaginase. Some patients also received total body, splenic, or testicular irradiation. Primary graft-versus-host disease (GVHD) prophylaxis was cyclosporine A and a corticosteroid.

Accelerated myeloid engraftment was associated with significant laboratory and clinical benefits. Compared to placebo, administration of LEUKINE significantly improved the following: time to neutrophil engraftment, duration of hospitalization, number of patients with bacteremia and overall incidence of infection (see **Table 4**).

Table 4

Allogeneic BMT: Analysis of Data from Placebo-Controlled Clinical Trial Median Values (days or number of patients)

	ANC ≥ 500/mm^3	ANC ≥ 1000/mm^3	Number of Patients with Infections	Number of Patients with Bacteremia	Days of Hospitalization
LEUKINE (n=53)	13*	14*	30*	9†	25*
Placebo (n=56)	17	19	42	19	26

*p <0.05 generalized Wilcoxon test

†p <0.05 simple chi-square test

Median time to myeloid engraftment (ANC ≥ 500 cells/mm^3) in 53 patients receiving LEUKINE was 4 four days less than in 56 patients treated with placebo (see **Table 4**). The number of patients with bacteremia and infection was significantly lower in the LEUKINE group compared to the placebo group (9/53 versus 19/56 and 30/53 versus 42/56, respectively). There were a number of secondary laboratory and clinical endpoints. Of these, only the incidence of severe (grade 3/4) mucositis was significantly improved in the LEUKINE group (4/53) compared to the placebo group (16/56) at p<0.05. LEUKINE-treated patients also had a shorter median duration of post-transplant IV antibiotic infusions, and shorter median number of days to last platelet and RBC transfusions compared to placebo patients, but none of these differences reached statistical significance.

Bone Marrow Transplantation Failure or Engraftment Delay

A historically-controlled study was conducted in patients experiencing graft failure following allogeneic or autologous BMT to determine whether LEUKINE improved survival after BMT failure.

Three categories of patients were eligible for this study:

1. patients displaying a delay in engraftment (ANC ≤ 100 cells/mm^3 by day 28 post-transplantation);
2. patients displaying a delay in engraftment (ANC ≤ 100 cells/mm^3 by day 21 post-transplantation) and who had evidence of an active infection; and
3. patients who lost their marrow graft after a transient engraftment (manifested by an average of ANC ≥ 500 cells/mm^3 for at least one week followed by loss of engraftment with ANC < 500 cells/mm^3 for at least one week beyond day 21 post-transplantation).

A total of 140 eligible patients from 35 institutions were treated with LEUKINE and evaluated in comparison to 103 historical control patients from a single institution. One hundred sixty-three patients had lymphoid or myeloid leukemia, 24 patients had non-Hodgkin's lymphoma, 19 patients had Hodgkin's disease and 37 patients had other diseases, such as aplastic anemia, myelodysplasia or non-hematologic malignancy. The majority of patients (223 out of 243) had received prior chemotherapy with or without radiotherapy and/or immunotherapy prior to preparation for transplantation.

One hundred day survival was improved in favor of the patients treated with LEUKINE after graft failure following either autologous or allogeneic BMT. In addition, the median survival was improved by greater than two-fold. The median survival of patients treated with LEUKINE after autologous failure was 474 days versus 161 days for the historical patients. Similarly, after allogeneic failure, the median survival was 97 days with LEUKINE treatment and 35 days for the historical controls. Improvement in survival was better in patients with fewer impaired organs.

The MOF score is a simple clinical and laboratory assessment of seven major organ systems: cardiovascular, respiratory, gastrointestinal, hematologic, renal, hepatic and neurologic.[10] Assessment of the MOF score is recommended as an additional method of determining the need to initiate treatment with LEUKINE in patients with graft failure or delay in engraftment following autologous or allogeneic BMT (see **Table 5**).

Table 5

Median Survival by Multiple Organ Failure (MOF) Category Median Survival (days)			
	MOF ≤ 2 Organs	**MOF > 2 Organs**	**MOF (Composite of Both Groups)**
Autologous BMT			
LEUKINE	474 (n=58)	78.5 (n=10)	474 (n=68)
Historical	165 (n=14)	39 (n=3)	161 (n=17)
Allogeneic BMT			
LEUKINE	174 (n=50)	27 (n=22)	97 (n=72)
Historical	52.5(n=60)	15.5(n=26)	35 (n=86)

Factors that Contribute to Survival

The probability of survival was relatively greater for patients with any one of the following characteristics: autologous BMT failure or delay in engraftment, exclusion of total body irradiation from the preparative regimen, a non-leukemic malignancy or MOF score ≤ two (zero, one or two dysfunctional organ systems). Leukemic subjects derived less benefit than other subjects.

CONTRAINDICATIONS

LEUKINE is contraindicated:

1. in patients with excessive leukemic myeloid blasts in the bone marrow or peripheral blood (≥ 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 preceding 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 for 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 ≥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 in **Table 6**.

Table 6

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			

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 in **Table 7**.

Table 7

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.

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 in **Table 8**.

Table 8

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

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 occurrence 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.

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme Corporation at 1-888-4RX-LEUKINE or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DOSAGE AND ADMINISTRATION

Neutrophil Recovery Following Chemotherapy in Acute Myelogenous Leukemia

The recommended dose is 250 mcg/m^2/day administered intravenously over a 4 hour period starting approximately on day 11 or four days following the completion of induction chemotherapy, if the day 10 bone marrow is hypoplastic with <5% blasts. If a second cycle of induction chemotherapy is necessary, LEUKINE should be administered approximately four days after the completion of chemotherapy if the bone marrow is hypoplastic with <5% blasts. LEUKINE should be continued until an ANC >1500 cells/mm^3 for 3 consecutive days or a maximum of 42 days. LEUKINE should be discontinued immediately if leukemic regrowth occurs. If a severe adverse reaction occurs, the dose can be reduced by 50% or temporarily discontinued until the reaction abates.

In order to avoid potential complications of excessive leukocytosis (WBC > 50,000 cells/mm^3 or ANC > 20,000 cells/mm^3) a CBC with differential is recommended twice per week during LEUKINE therapy. LEUKINE treatment should be interrupted or the dose reduced by half if the ANC exceeds 20,000 cells/mm^3.

Mobilization of Peripheral Blood Progenitor Cells

The recommended dose is 250 mcg/m^2/day administered IV over 24 hours or SC once daily. Dosing should continue at the same dose through the period of PBPC collection. The optimal schedule for PBPC collection has not been established. In clinical studies, collection of PBPC was usually begun by day 5 and performed daily until protocol specified targets were achieved (see **CLINICAL EXPERIENCE**, **Mobilization and Engraftment of PBPC**). If WBC > 50,000 cells/mm^3, the LEUKINE dose should be reduced by 50%. If adequate numbers of progenitor cells are not collected, other mobilization therapy should be considered.

Post Peripheral Blood Progenitor Cell Transplantation

The recommended dose is 250 mcg/m^2/day administered IV over 24 hours or SC once daily beginning immediately following infusion of progenitor cells and continuing until an ANC>1500 cells/mm^3 for three consecutive days is attained.

Myeloid Reconstitution After Autologous or Allogeneic Bone Marrow Transplantation

The recommended dose is 250 mcg/m^2/day administered IV over a 2-hour period beginning two to four hours after bone marrow infusion, and not less than 24 hours after the last dose of chemotherapy or radiotherapy. Patients should not receive LEUKINE until the post marrow infusion ANC is less than 500 cells/mm^3. LEUKINE should be continued until an ANC >1500 cells/mm^3 for three consecutive days is attained. If a severe adverse reaction occurs, the dose can be reduced by 50% or temporarily discontinued until the reaction abates. LEUKINE should be discontinued immediately if blast cells appear or disease progression occurs.

In order to avoid potential complications of excessive leukocytosis (WBC > 50,000 cells/mm^3, ANC > 20,000 cells/mm^3) a CBC with differential is recommended twice per week during LEUKINE therapy. LEUKINE treatment should be interrupted or the dose reduced by 50% if the ANC exceeds 20,000 cells/mm^3.

Bone Marrow Transplantation Failure or Engraftment Delay

The recommended dose is 250 mcg/m^2/day for 14 days as a 2-hour IV infusion. The dose can be repeated after 7 days off therapy if engraftment has not occurred. If engraftment still has not occurred, a third course of 500 mcg/m^2/day for 14 days may be tried after another 7 days off therapy. If there is still no improvement, it is unlikely that further dose escalation will be beneficial. If a severe adverse reaction occurs, the dose can be reduced by 50% or temporarily discontinued until the reaction abates. LEUKINE should be discontinued immediately if blast cells appear or disease progression occurs.

In order to avoid potential complications of excessive leukocytosis (WBC > 50,000 cells/mm^3, ANC > 20,000 cells/mm^3) a CBC with differential is recommended twice per week during LEUKINE therapy. LEUKINE treatment should be interrupted or the dose reduced by half if the ANC exceeds 20,000 cells/mm^3.

Preparation of LEUKINE

1. Liquid LEUKINE is formulated as a sterile, preserved (1.1% benzyl alcohol), injectable solution (500 mcg/mL) in a vial. Lyophilized LEUKINE is a sterile, white, preservative-free powder (250 mcg) that requires reconstitution with 1 mL Sterile Water for Injection, USP, or 1 mL Bacteriostatic Water for Injection, USP.
2. Liquid LEUKINE may be stored for up to 20 days at 2–8°C once the vial has been entered. Discard any remaining solution after 20 days.
3. Lyophilized LEUKINE (250 mcg) should be reconstituted aseptically with 1.0 mL of diluent (see below). The contents of vials reconstituted with different diluents should not be mixed together. *Sterile Water for Injection, USP (without preservative):* Lyophilized LEUKINE vials contain no antibacterial preservative, and therefore solutions prepared with Sterile Water for Injection, USP should be administered as soon as possible, and within 6 hours following reconstitution and/or dilution for IV infusion. The vial should not be re-entered or reused. Do not save any unused portion for administration more than 6 hours following reconstitution. *Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol):* Reconstituted solutions prepared with Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol) may be stored for up to 20 days at 2–8°C prior to use. Discard reconstituted solution after 20 days. Previously reconstituted solutions mixed with freshly reconstituted solutions must be administered within 6 hours following mixing. **Preparations containing benzyl alcohol (including liquid LEUKINE and lyophilized LEUKINE reconstituted with Bacteriostatic Water for Injection) should not be used in neonates** (see **WARNINGS**).
4. During reconstitution of lyophilized LEUKINE the diluent should be directed at the side of the vial and the contents gently swirled to avoid foaming during dissolution. Avoid excessive or vigorous agitation; do not shake.
5. LEUKINE should be used for SC injection without further dilution. Dilution for IV infusion should be performed in 0.9% Sodium Chloride Injection, USP. If the final concentration of LEUKINE is below 10 mcg/mL, Albumin (Human) at a final concentration of 0.1% should be added to the saline prior to addition of LEUKINE to prevent adsorption to the components of the drug delivery system. To obtain a final concentration of 0.1% Albumin (Human), add 1 mg Albumin (Human) per 1 mL 0.9% Sodium Chloride Injection, USP (e.g., use 1 mL 5% Albumin [Human] in 50 mL 0.9% Sodium Chloride Injection, USP).
6. An in-line membrane filter should NOT be used for intravenous infusion of LEUKINE.
7. Store liquid LEUKINE and reconstituted lyophilized LEUKINE solutions under refrigeration at 2–8°C (36–46°F); DO NOT FREEZE.
8. In the absence of compatibility and stability information, no other medication should be added to infusion solutions containing LEUKINE. Use only 0.9% Sodium Chloride Injection, USP to prepare IV infusion solutions.
9. Aseptic technique should be employed in the preparation of all LEUKINE solutions. To assure correct concentration following reconstitution, care should be exercised to eliminate any air bubbles from the needle hub of the syringe used to prepare the diluent. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter is present or the solution is discolored, the vial should not be used.

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:

Lyophilized LEUKINE

Carton of five vials of lyophilized LEUKINE 250 mcg (NDC 0024-5843-05)

Liquid LEUKINE

Carton of one multiple-use vial; each vial contains 1 mL of preserved 500 mcg/mL liquid LEUKINE (NDC 0024-5844-01)

Carton of five multiple-use vials; each vial contains 1 mL of preserved 500 mcg/mL liquid LEUKINE (NDC 0024-5844-05)

STORAGE

LEUKINE should be refrigerated at 2–8°C (36–46°F). Do not freeze or shake. Do not use beyond the expiration date printed on the vial.

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Revised April 2013

LEUKINE® (SARGRAMOSTIM)

A RECOMBINANT GM-CSF - YEAST-EXPRESSED

INFORMATION FOR PATIENTS

This patient package insert is for the injection of liquid LEUKINE.

IMPORTANT NOTE*:* Please read ALL information about LEUKINE in this Patient Information Leaflet before administering any injections.

This patient package insert contains information and directions for patients and their caregivers who are receiving or giving injections of LEUKINE at home. This package insert is intended to supplement discussions with your healthcare provider and does not take the place of talking with your doctor, nurse or pharmacist. If you have any questions about your treatment with LEUKINE, be sure to discuss them with your healthcare team.

LEUKINE ACTIONS AND USES

LEUKINE (loo'-kine) is the brand name of sargramostim (sar-gram'-oh-stim) and is also known as granulocyte-macrophage colony-stimulating factor, or GM-CSF for short. LEUKINE is a man-made form of a protein, called a growth factor, that is almost identical to a protein your body makes when it is functioning normally. This growth factor helps to increase the number and function of your white blood cells, specifically neutrophils, monocytes/macrophages, and myeloid-derived dendritic cells. White blood cells, which are made in your bone marrow (the soft center of your bone), fight infections from bacteria, fungi, and viruses by surrounding and destroying them. White blood cells also help to repair tissues by removing dead and damaged cells.

If your white blood cell count (the number of white blood cells in your blood) falls to a very low level, your chance of getting an infection increases. The purpose of using LEUKINE is to help your bone marrow make more white blood cells, which in turn can help your immune system recover.

LEUKINE is used to help increase the number and function of white blood cells after bone marrow transplantation, in cases of bone marrow transplantation failure or engraftment delay, before and after peripheral blood stem cell transplantation, and following induction chemotherapy in older patients with acute myelogenous leukemia. Your doctor may also choose to treat other conditions with LEUKINE.

Your doctor has prescribed LEUKINE for you. If you are also receiving chemotherapy or radiation therapy, do not take your LEUKINE in the period 24 hours before through 24 hours after the administration of your chemotherapy or radiation therapy. You may also need a blood test so that your doctor can monitor your white blood cell count and, if necessary, adjust your LEUKINE dose.

POSSIBLE SIDE EFFECTS

Some patients taking LEUKINE may experience unwanted side effects, most of which are mild to moderate and not serious. Not everyone who receives LEUKINE will experience side effects. Some of the more common side effects include bone pain, feeling like you have the flu, feeling tired or weak, muscle aches, diarrhea, or stomach upset. You may also get a low fever (less than 100.5° F or 38° C) about one to four hours after an injection, or you may have swelling, redness, and/or discomfort where LEUKINE is injected. Your doctor, nurse, or pharmacist will tell you about other possible side effects. Many of these side effects can be reduced or eliminated. Talk to your doctor, nurse, or pharmacist about what you should do if any of these things happen to you.

Some side effects or symptoms may be serious. These may be due to LEUKINE, your illness, or other treatments you may have received. Call your doctor immediately if any of the following happen to you:

- You develop a high fever (over 100.5° F or 38° C).
- You notice any signs of infection including chills, sore throat, or congestion (such as a stuffy nose).
- You have trouble breathing, or you develop wheezing, fainting, extensive skin rash, hives, or feel you are having an allergic reaction (see ALLERGY TO LEUKINE section below).
- You experience sudden weight gain or other signs of fluid build-up such as swollen legs or feet.
- You develop chest pain, chest discomfort, or a rapid or irregular pulse.

If you are concerned about any other side effects or symptoms you may be having, contact your doctor, nurse, or pharmacist.

ALLERGY TO LEUKINE

A generalized allergy is an uncommon but potentially serious reaction to LEUKINE. This may include a skin rash over your entire body, hives, trouble breathing, a fast pulse, sweating, and feeling faint. In severe cases a generalized allergy may be life-threatening. If you think you are having a generalized allergy to LEUKINE, stop taking LEUKINE and notify your doctor immediately.

USAGE IN PREGNANCY AND BREAST FEEDING

If you are pregnant, are trying to become pregnant, or are breast-feeding, you should consult your doctor before taking LEUKINE.

STORAGE OF LEUKINE

LEUKINE should be stored in the refrigerator but not in the freezer compartment. Do not shake LEUKINE. Do not use LEUKINE that has been frozen. Keep LEUKINE out of direct sunlight. Do not use LEUKINE beyond the expiration date printed on the vial label. Once the vial has been used, any remaining LEUKINE should be stored in the refrigerator and used within 20 days (be sure to mark down the date you first used the vial). Throw away any remaining LEUKINE after 20 days.

INSTRUCTIONS FOR PREPARING AND GIVING A SELF-INJECTION

Use the correct syringe and dose

If your doctor has recommended that you take LEUKINE at home, your doctor, nurse, or pharmacist should have instructed you and/or your caregiver on how LEUKINE should be prepared, how it should be injected, and how often it should be injected.

The dose will usually be measured in milliliters (mL) or cubic centimeters (cc). (For example: 0.8 mL or 0.8 cc). It is important that you use a syringe that is marked in tenths (1/10) of a milliliter or cubic centimeter (for example: 0.1, 0.2, 0.3, 0.4, 0.5, etc. ... to 1.0 mL or cc) so that you are able to measure the correct dose prescribed by your doctor. A 3 cc syringe with a 25 to 30 gauge 5/8-inch needle or the syringe and needle size specified by your doctor may be used. Your doctor will either supply you with the correct syringes and needles, or will write you a prescription so you can get the correct syringes and needles from your pharmacy.

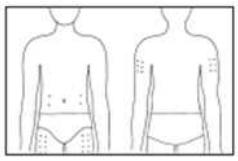
It is very important that you use the correct needle and syringe. Failure to use the correct syringe could result in your receiving either too little or too much LEUKINE. If you receive too little LEUKINE, it may not be effective. If you receive too much LEUKINE, your white blood cell count may get too high, which may be harmful.

Your dose has been selected to meet your individual needs. Do not change your dose without consulting your doctor. If you are not sure about the amount (mL or cc) or dose to be used, talk to your doctor, nurse, or pharmacist.

INJECTION SITE

Choosing an Injection Site

Your doctor, nurse, or pharmacist has instructed you on how to give yourself a subcutaneous (under the skin) injection of LEUKINE. The best areas for self-injecting LEUKINE are the thighs or stomach. The navel and waistline should be avoided. If a caregiver is helping with the injections, you may be instructed to inject on the back portion of the upper arms. It is a good idea to know where your injection will be given before you prepare your dose.



Rotating Injection Sites

It is important to use a different injection site each time to avoid soreness in any one area. A new injection should not be given in the same area as the last injection. It is a good idea to alternate your injection sites from one thigh to the stomach and then to the other thigh. This is called rotating your injection sites. Injection sites should be at least one inch apart. Do not choose an area where the skin is tender, bruised, red, or hard. To keep track of your injection sites, keep a record of where and when you give yourself an injection. One way to do that is to note the injection site on a calendar or in a diary along with the date you first used the vial. If all areas become tender, talk to your doctor, nurse, or pharmacist about choosing other injection sites.

Injection Site Skin Reactions

Occasionally a skin reaction may occur at the injection site. This usually will not require you to stop taking LEUKINE. The skin may become red, painful, or swollen. If a skin reaction occurs, contact your doctor. The following steps may be taken to help prevent further skin reactions:

- At least 30 minutes before you plan to inject, remove your LEUKINE from the refrigerator and allow it to come to room temperature before injecting.
- Rotate the injection sites from one injection to the next.
- Apply ice to the site for one minute immediately prior to injection.
- Inject LEUKINE slowly.
- Avoid rubbing the skin before or after injecting.

GIVING YOURSELF AN INJECTION

Before using LEUKINE for the first time, talk to your doctor, nurse, or pharmacist about how to use it, what to expect when using it, possible side effects, and what to do if side effects occur. You must be instructed and trained properly in how to prepare and inject LEUKINE by your doctor, nurse, or pharmacist prior to using it. Do not attempt to self-administer LEUKINE until you are sure that you understand the instructions for giving an injection to yourself. Your dose has been selected to meet your individual needs. Do not change your dose without consulting your doctor. If you are unsure about the amount (mL or cc) or dose to be used, how to inject yourself, or how often to inject yourself, talk to your doctor, nurse, or pharmacist.

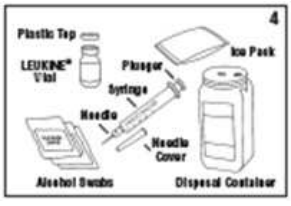
IMPORTANT: IT IS VERY IMPORTANT THAT YOU CAREFULLY READ THESE INSTRUCTIONS AND FOLLOW THEM EXACTLY IN ORDER TO HELP AVOID CONTAMINATION OF THE LEUKINE AND POSSIBLE INFECTION.

Remove LEUKINE From the Refrigerator and Inspect the Vial and Contents

1. Take the LEUKINE vial out of the refrigerator at least 30 minutes before you plan to inject, allowing it to come to room temperature. Do not leave the vial in direct sunlight.
2. Check the date on the label to make sure the LEUKINE has not expired; if it has, contact your doctor, nurse, or pharmacist for further instructions. LEUKINE should be clear and colorless. If it is not, or if the LEUKINE appears to contain lumps, flakes, or particles, contact your doctor, nurse, or pharmacist.
3. **DO NOT SHAKE** the vial. Shaking the vial could cause froth or bubbles to appear. Although this will not affect how well LEUKINE will work, it could decrease the amount of LEUKINE that you are able to draw into the syringe. If the LEUKINE looks frothy or bubbly, use another vial. Return the frothy or bubbly vial to the refrigerator and allow it to settle for use on another day.

Gather Your Supplies and Prepare Your Work Area

4. Select a clean, convenient, well-lit location to lay out your supplies. It is a good idea to wipe down the area with an alcohol swab to make sure it is germ-free. Gather the following supplies along with the LEUKINE:
   - A sterile syringe and needle (as specified by your doctor, nurse, or pharmacist)
   - Prepackaged alcohol swabs
   - Ice pack
   - A puncture-resistant container for disposal of the needle and syringe (see Step 22 regarding proper disposal container)



Choose and Prepare the Injection Site

5. Wash your hands thoroughly with soap and warm water, and dry them with a clean towel.
   This should be done just before cleaning the injection site and preparing the LEUKINE dose.

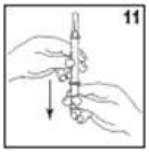
6. Choose an injection site. Do not choose an area where the skin is tender, bruised, red, or hard. As you have been instructed, choose a different site with each injection. Today's injection should not be given in the same area as your last injection. To keep track of your injection sites, you may want to record the injection site you picked on a calendar or in a diary. For additional information, please refer to the INJECTION SITE section above.
7. Ice the site for about 1 minute before your injection. Then, with an alcohol swab, wipe the skin where the injection will be made using a gentle circular motion. Allow the skin to dry for about 10 seconds. Set the used alcohol swab aside. Do not re-use this alcohol swab.

Withdraw the LEUKINE From the Vial

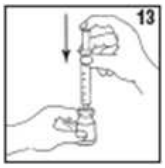
8. The LEUKINE should now be at room temperature. DO NOT SHAKE the vial.
9. Flip off the plastic cap from the LEUKINE vial. Do not remove the gray rubber stopper.

10. Wipe the top of the rubber stopper with a new alcohol swab. Set the used alcohol swab aside. Do not touch the rubber stopper with your hands or fingers. If you do touch the stopper, clean it again with a new alcohol swab.

11. Remove the syringe and needle specified by your doctor from its packaging. With the cover still on the needle, draw air into the syringe by pulling back on the plunger. The amount of air you draw into the syringe should be equal to your LEUKINE dose.



12. Carefully remove the needle cover. Do not lay down the syringe or allow the needle to touch anything. If the needle touches any surface, including your hands, throw away the needle and syringe in your disposal container and start over (at Step 11) with a new syringe and needle.
13. With the vial **upright**, insert the needle downward, through the center of the gray rubber stopper. After the needle penetrates the gray rubber stopper, push the plunger all the way in to inject the air into the vial. Make sure the needle is above the LEUKINE. Try not to inject the air into the LEUKINE because bubbles may form, making it hard for you to withdraw the correct LEUKINE dose. The air you just injected into the vial will make it easier for you to withdraw the LEUKINE into the syringe. Leave the needle in the rubber stopper.



14. Without withdrawing the needle from the rubber stopper, turn the vial **upside down.** Then, move the needle tip into the LEUKINE. Now slowly pull back on the plunger until the correct dose of LEUKINE is in the syringe.

15. Before withdrawing the needle from the rubber stopper, be sure there are no air bubbles in the syringe. The air bubbles are harmless but they can decrease the amount of LEUKINE you receive. If there are air bubbles, gently tap the syringe with your fingers until the air bubbles rise to the top of the syringe. To remove air bubbles, gently push some of the solution back into the vial. Now slowly pull back on the plunger until the correct dose of LEUKINE is in the syringe. Repeat this procedure as needed until you can draw up the correct dose of LEUKINE without air bubbles.
16. Withdraw the needle from the rubber stopper. Do not lay down the syringe or allow the needle to touch anything.

Inject the LEUKINE

17. With one hand, gently smooth the skin of the injection site (the area you wiped with the alcohol swab) between your thumb and forefinger so it is taut.

18. With your other hand, hold the syringe, just like a pencil, at a 90 degree angle to the skin, about 2 inches above the surface of the skin. Using a quick, short motion, insert the needle.

19. Release your grasp on the skin. Gently pull back on the plunger just a little bit (about 1/8 of an inch). If you do not see blood in the syringe, slowly inject all of the LEUKINE by pushing the plunger all the way down.
    If you see blood in the syringe, do not inject LEUKINE. Withdraw the needle at the same angle it was inserted. Finding blood in the syringe simply means you hit a blood vessel rather than the fatty tissues you need to inject into, and is not a cause for concern. Discard the syringe in a puncture-resistant container. Repeat the steps to prepare a new syringe. Choose, clean, and ice a new

injection site. Remember to check again for blood before injecting LEUKINE.

20. Remove the needle at the same angle as it was inserted.
21. Lightly touch an alcohol swab over the injection site until any bleeding has stopped. Do not rub or press the site because doing so may irritate the skin.

Dispose of Supplies

22. It is extremely important that you do not reuse syringes or needles. Do not attempt to put the needle cover back on the needle. Throw away used syringes and needles in a puncture-resistant container as instructed by your doctor, nurse, or pharmacist. They may be able to supply you with a container made specifically for disposing of used syringes and needles. If not, then you may use the following:
    - A hard plastic container that you cannot see through with a screw-on cap, such as an empty bleach or laundry detergent bottle. Always screw the cap on tightly after disposing of your syringes and needles. Do not recycle the container.
    - A metal container with a plastic lid, such as a coffee can. Cut a hole in the plastic lid and tape the lid to the metal container
    - DO NOT use a glass or clear plastic container, or any container that will be recycled or returned to a store.

23. Keep the container out of the reach of children. Make sure the container is properly labeled as to its content. When the container is about two-thirds (2/3) full, dispose of it as instructed. There may be special state and local laws regarding the proper disposal of needles and syringes that your doctor, nurse, or pharmacist may discuss with you.
24. Throw away empty LEUKINE vials and used alcohol swabs in the trash, unless otherwise instructed.
25. **If the vial has any remaining LEUKINE, return the used vial to the refrigerator for use the next day. Do not freeze. Used vials containing LEUKINE should be stored in the refrigerator and used within 20 days (be sure to mark down the date you first used the vial). After 20 days, throw away any remaining LEUKINE.**

IMPORTANT NOTES

1. Follow the instructions given to you by your doctor, nurse, or pharmacist. Do not make any changes in your dose or how often you give yourself LEUKINE. If you are not sure about the amount (mL or cc) or dose to be used, talk to your doctor, nurse, or pharmacist.
2. Try to get into a routine; give yourself LEUKINE at the same time each day.
3. Keep LEUKINE and all supplies out of the reach of children.
4. If any of the following happens to you, contact your doctor, nurse, or pharmacist:
    - You miss a dose of LEUKINE.
    - You notice anything unusual about your condition while you are taking LEUKINE.
    - You develop a high fever (over 100.5° F or 38° C).
    - You notice any signs of infection, including chills, sore throat, or congestion (such as a stuffy nose).

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