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LEUKINE®
SARGRAMOSTIM

Rx only

BERLEX®

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 3 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 LEUKINE Liquid presentation is formulated as a sterile, preserved (11% 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.

LEUKINE Liquid and reconstituted lyophilized LEUKINE are clear, colorless liquids suitable for subcutaneous injection or intravenous infusion. LEUKINE Liquid contains 500 mcg (2.8 x 10^6 IU/mL) sargramostim and 11% benzyl alcohol in a 1 mL solution. The vial of lyophilized LEUKINE contains 250 mcg (1.4 x 10^6 IU/vial) sargramostim. The LEUKINE Liquid 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 x 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.

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 granulocytic, pure macrophage and mixed granulocyte-macrophage 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[5] 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 (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.[2]

When LEUKINE (either liquid or lyophilized) was administered IV over 2 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 LEUKINE Liquid, 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 3 or 6 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 1 to 3 hours post injection, and LEUKINE remained detectable for up to 6 hours after injection. The mean Cmax was 1.5 ng/mL. For LEUKINE Liquid, 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.

Antibody Formation Serum samples collected before and after LEUKINE treatment from 214 patients with a variety of underlying diseases have been examined for the presence of antibodies. Neutralizing antibodies were detected in 5 of 214 patients (2.3%) after receiving LEUKINE by continuous IV infusion (3 patients) or subcutaneous injection (2 patients) for 28 to 84 days in multiple courses. All 5 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. 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.

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 Progenitor 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 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 ≤ 2 (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 sargramostim 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 4 days following the second cycle of induction chemotherapy, LEUKINE (250 mcg/m^2/day) or placebo was given IV over 4 hours each day, starting 4 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 (sargramostim) significantly shortened the median duration of ANC <500/mm^3 by 4 days and <1000/mm^3 by 7 days following induction (see table at right). 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 1 cycle (70%) or 2 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.

Hematological Recovery (in Days): Induction

	sargramostim n=52*	Placebo n=47	
Dataset	Median (25%, 75%)	Median (25%, 75%)	p-value**
ANC>500/mm^3 [a]	13 (11, 16)	17 (13, 25)	0.009
ANC>1000/mm^3 [b]	14 (12, 18)	21 (13, 34)	0.003
PLT>20000/mm^3 [c]	11 (7, 14)	12 (9, >42)	0.10
RBC[c]	12 (9, 24)	14 (9, 42)	0.53

* *Patients with missing data censored.*
[a] *2 patients on sargramostim and 4 patients on placebo had missing values.*
[b] *2 patients on sargramostim and 3 patients on placebo had missing values.*
[c] *4 patients on placebo had missing values.*
[c] *3 patients on sargramostim and 4 patients on placebo had missing values.*
** *p=Generalized Wilcoxon*

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 sargramostim 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 5 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=.017). 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. Leukapheresses were initiated for all mobilization groups after the WBC reached 10000/mm^3. Leukapheresis 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 10000 cells/mm^3 by day 5, 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 1141 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 at right). 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.

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 250 mcg/m^2 IV	no	21	24
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 non-mobilized 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 3 studies. The majority of the patients had lymphoid malignancy (87 NHL, 17 ALL). 23 patients had Hodgkin's disease, and 1 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 3 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 3 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 2 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 2 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 3 studies revealed that the median time to engraftment for patients with Hodgkin's disease, regardless of treatment, was 6 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 3 studies, these 2 subgroups (NHL and ALL vs. Hodgkin's disease) are presented separately.

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WARNINGS

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Sandoz Inc. IPR2016-0
Sandoz v. Eli Lilly, Exhibit 1089-

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WARNINGS (continued)

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 (sargramostim) 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 3 to 7 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.

Patient 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 women 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 60-1000 mcg/m^2/day intravenously and 4-1500 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 LEUKINE Liquid) 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 3 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.

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	26	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			

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 (sargramostim) 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.

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	60	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.*

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=0007), low serum proteins and prolonged prothrombin time (p=002) 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=0016), liver function abnormalities (p=0.006), and neurocortical hemorrhagic events (p=0.025).[16]

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	26	**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

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 (4000 mcg/m^2/day or 16 times the recommended dose) were administered to 4 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.

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 4 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 4 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 > 50000 cells/mm^3 or ANC > 20000 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 20000 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 biegrattment of PBPC). If WBC > 50000 cells/mm3, 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 Blo
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In order to avoid p
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Preparation of LEU

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HOW SUPPLIE

LEUKINE Liquid is ava
(1.4 x 10^6 IU/vial) ser

Carton of 5 vials
Carton of 5 multip

STORAGE

LEUKINE should be re

REFERENCES

1. Metcalf D. The m
2. Park LS, Friend D
164:251-262.
3. Grabstein KH, Urd
232:506-508.
4. Reed SG, Nathan
hydrogen peroxide
5. Data on file Berlex
6. Howe JM, Anderso
(>55 to 70 years o
7. Nemunaitis J, Rab
lymphoid malignan
8. Nemunaitis J, Sin
for lymphoid malig
9. Nemunaitis J, Sin
autologous bone m
10. Goris RJA, Boekh
11. Burm P, Crowley J
lung cancer: a pro
12. Herrmann F, Schu
Institute Research
13. Estey EH, Dixon D
macrophage colon
14. Vadhan-Raj S, Ke
syndromes. NEJM
15. Buchner T, Hidder
myeloid leukemia
16. Blazar BR, Kersey
leukemia patients

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Sandoz Inc. IPR2016-0
Sandoz v. Eli Lilly, Exhibit 1089-

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