

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LEUKINE safely and effectively. See full prescribing information for LEUKINE.

LEUKINE® (sargramostim) for injection, for subcutaneous or intravenous use

LEUKINE® (sargramostim) injection, for subcutaneous or intravenous use
Initial U.S. Approval: 1991

RECENT MAJOR CHANGES

Indications and Usage (1.5, 1.6)	03/2018
Dosage and Administration (2.6)	03/2018
Contraindications (4)	03/2018
Warnings and Precautions (5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.9)	03/2018

INDICATIONS AND USAGE

LEUKINE is a leukocyte growth factor indicated:

- To shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death following induction chemotherapy in adult patients 55 years and older with acute myeloid leukemia (AML). (1.1)
- For the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis and autologous transplantation in adult patients. (1.2)
- For the acceleration of myeloid reconstitution following autologous bone marrow or peripheral blood progenitor cell transplantation in adult and pediatric patients 2 years of age and older. (1.3)
- For the acceleration of myeloid reconstitution following allogeneic bone marrow transplantation in adult and pediatric patients 2 years of age and older. (1.4)
- For treatment of delayed neutrophil recovery or graft failure after autologous or allogeneic bone marrow transplantation in adult and pediatric patients 2 years of age and older. (1.5)
- To increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [H-ARS]). (1.6)

DOSAGE AND ADMINISTRATION

See Full Prescribing Information for dosage adjustments and timing of administration (2.1-2.6).

- AML, Neutrophil recovery following chemotherapy:
 - 250 mcg/m²/day administered intravenously over a 4-hour period. (2.1)
- Mobilization of peripheral blood progenitor cells:
 - 250 mcg/m²/day administered intravenously over 24 hours or subcutaneous injection once daily. (2.2)
- Post peripheral blood progenitor cell transplantation:
 - 250 mcg/m²/day administered intravenously over 24 hours or subcutaneous injection once. (2.3)
- Myeloid reconstitution after autologous or allogeneic BMT:
 - 250 mcg/m²/day administered intravenously over a 2-hour period. (2.4)
- BMT failure or engraftment delayed:
 - 250 mcg/m²/day for 14 days as a 2-hour intravenous infusion. (2.5)
- Patients acutely exposed to myelosuppressive doses of radiation, administer once daily as subcutaneous injection:
 - Adults and pediatric patients weighing >40 kg: 7 mcg/kg
 - Pediatric patients 15 kg to 40 kg: 10 mcg/kg
 - Pediatric patients <15 kg: 12 mcg/kg (2.6)

DOSAGE FORMS AND STRENGTHS

- For injection (lyophilized powder): 250 mcg of sargramostim in single-dose vial for reconstitution (3)
- Injection (solution): 500 mcg per mL sargramostim in multiple-dose vial (3)

CONTRAINDICATIONS

- Do not administer LEUKINE to patients with a history of serious allergic reactions, including anaphylaxis, to human granulocyte-macrophage colony stimulating factor such as sargramostim, yeast-derived products, or any component of the product. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Permanently discontinue LEUKINE in patients with serious allergic reactions. (5.1)
- Infusion Related Reactions: Manage using infusion rate reductions or discontinuations. (5.2)
- Effusions and Capillary Leak Syndrome: Manage with dose-reduction, discontinuation, or diuretics. Monitor body weight and hydration status during therapy. (5.4)
- Supraventricular Arrhythmias: Risk may be increased in patients with history of cardiac arrhythmias. Manage medically and discontinue LEUKINE. (5.5)

ADVERSE REACTIONS

The most common adverse reactions (incidence >30%) were (6.1):

- In recipients of autologous BMT: fever, nausea, diarrhea, vomiting, mucous membrane disorder, alopecia, asthenia, malaise, anorexia, rash, gastrointestinal disorder and edema.
- In recipients of allogeneic BMT: diarrhea, fever, nausea, rash, vomiting, stomatitis, anorexia, high glucose, alopecia, abdominal pain, low albumin, headache and hypertension.
- In patients with AML: fever, liver toxicity, skin reactions, infections, metabolic laboratory abnormalities, nausea, diarrhea, genitourinary abnormalities, pulmonary toxicity, vomiting, neurotoxicity, stomatitis, alopecia and weight loss.

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

DRUG INTERACTIONS

- Use with caution in patients receiving drugs that may potentiate LEUKINE's myeloproliferative effects, such as lithium and corticosteroids (7.1)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Benzyl alcohol-free formulation recommended. May cause fetal harm. (8.1)
- Pediatrics: In infants, avoid use of benzyl alcohol-containing solutions when feasible. (2.7, 5.9, 8.4)
- Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 05/2018

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- Allogeneic or Autologous Bone Marrow Transplantation: Treatment of Delayed Neutrophil Recovery or Graft Failure
- Acute Exposure to Myelosuppressive Doses of Radiation (H-ARS)

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- Autologous Peripheral Blood Progenitor Cell Mobilization and Collection
- Autologous Peripheral Blood Progenitor Cell and Bone Marrow Transplantation
- Allogeneic Bone Marrow Transplantation

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Acute Myeloid Leukemia Following Induction Chemotherapy

LEUKINE is indicated to shorten time to neutrophil recovery and to reduce the incidence of severe, life-threatening, or fatal infections following induction chemotherapy in adult patients 55 years and older with acute myeloid leukemia (AML).

1.2 Autologous Peripheral Blood Progenitor Cell Mobilization and Collection

LEUKINE is indicated in adult patients with cancer undergoing autologous hematopoietic stem cell transplantation for the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis.

1.3 Autologous Peripheral Blood Progenitor Cell and Bone Marrow Transplantation

LEUKINE is indicated for the acceleration of myeloid reconstitution following autologous peripheral blood progenitor cell (PBPC) or bone marrow transplantation in adult and pediatric patients 2 years of age and older with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) and Hodgkin's lymphoma (HL).

1.4 Allogeneic Bone Marrow Transplantation

LEUKINE is indicated for the acceleration of myeloid reconstitution in adult and pediatric patients 2 years of age and older undergoing allogeneic bone marrow transplantation from HLA-matched related donors.

1.5 Allogeneic or Autologous Bone Marrow Transplantation: Treatment of Delayed Neutrophil Recovery or Graft Failure

LEUKINE is indicated for the treatment of adult and pediatric patients 2 years and older who have undergone allogeneic or autologous bone marrow transplantation in whom neutrophil recovery is delayed or failed.

1.6 Acute Exposure to Myelosuppressive Doses of Radiation (H-ARS)

LEUKINE is indicated to increase survival in adult and pediatric patients from birth to 17 years of age acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [H-ARS]).

2 DOSAGE AND ADMINISTRATION

2.1 Neutrophil Recovery Following Induction Chemotherapy for Acute Myeloid Leukemia

The recommended dose is 250 mcg/m²/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 less than 5% blasts. If a second cycle of induction chemotherapy is necessary, administer LEUKINE approximately four days after the completion of chemotherapy if the bone marrow is hypoplastic with less than 5% blasts. Continue LEUKINE until an absolute neutrophil count (ANC) greater than 1500 cells/mm³ for 3 consecutive days or a maximum of 42 days. Do not administer LEUKINE within 24 hours

preceding or following receipt of chemotherapy or radiotherapy [see *Warnings and Precautions (5.3)*].

Dose Modifications

Obtain a CBC with differential twice per week during LEUKINE therapy and modify the dose for the following:

- Leukemic regrowth: Discontinue LEUKINE immediately
- Grade 3 or 4 adverse reactions: Reduce the dose of LEUKINE by 50% or interrupt dosing until the reaction abates
- ANC greater than 20,000 cells/mm³: Interrupt LEUKINE treatment or reduce the dose by 50%

2.2 Autologous Peripheral Blood Progenitor Cell Mobilization and Collection

The recommended dose is 250 mcg/m²/day administered intravenously over 24 hours or subcutaneously once daily. 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 after 5 days of LEUKINE and performed daily until protocol specified targets were achieved [see *Clinical Studies (14)*].

If WBC greater than 50,000 cells/mm³, reduce the LEUKINE dose by 50%. Consider other mobilization therapy if adequate numbers of progenitor cells are not collected.

2.3 Autologous Peripheral Blood Progenitor Cell and Bone Marrow Transplantation

Autologous Peripheral Blood Progenitor Cell Transplantation

The recommended dose is 250 mcg/m²/day administered intravenously over 24 hours or subcutaneously once daily beginning immediately following infusion of progenitor cells and continuing until an ANC greater than 1500 cells/mm³ for three consecutive days is attained. Do not administer LEUKINE within 24 hours preceding or following receipt of chemotherapy or radiotherapy.

Autologous Bone Marrow Transplantation

The recommended dose is 250 mcg/m²/day administered intravenously 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. Do not administer LEUKINE until the post marrow infusion ANC is less than 500 cells/mm³. Continue LEUKINE until an ANC greater than 1500 cells/mm³ for three consecutive days is attained. Do not administer LEUKINE within 24 hours preceding or following receipt of chemotherapy or radiotherapy [see *Warnings and Precautions (5.3)*].

2.4 Allogeneic Bone Marrow Transplantation

The recommended dose is 250 mcg/m²/day administered intravenously 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. Do not administer LEUKINE until the post marrow infusion ANC is less than 500 cells/mm³. Continue LEUKINE until an ANC greater than 1500 cells/mm³ for three consecutive days is attained. Do not administer LEUKINE within 24 hours

preceding or following receipt of chemotherapy or radiotherapy [see *Warnings and Precautions (5.3)*].

Dose Modifications

Obtain a CBC with differential twice per week during LEUKINE therapy and modify the dose as for the following:

- Disease progression or blast cell appearance: Discontinue LEUKINE immediately
- Grade 3 or 4 adverse reactions: Reduce the dose of LEUKINE by 50% or temporarily discontinue until the reaction abates
- WBC greater than 50,000 cells/mm³ or ANC greater than 20,000 cells/mm³: Interrupt LEUKINE treatment or reduce the dose by 50%

2.5 Allogeneic or Autologous Bone Marrow Transplantation: Treatment of Delayed Neutrophil Recovery or Graft Failure

The recommended dose is 250 mcg/m²/day for 14 days as a 2-hour intravenous infusion. The dose can be repeated after 7 days off therapy if neutrophil recovery has not occurred. If neutrophil recovery still has not occurred, a third course of 500 mcg/m²/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.

Dose Modifications

Obtain a CBC with differential twice per week during LEUKINE therapy and modify the dose as for the following:

- Disease progression or blast cell appearance: Discontinue LEUKINE immediately
- Grade 3 or 4 adverse reactions: Reduce the dose of LEUKINE by 50% or temporarily discontinue until the reaction abates
- WBC greater than 50,000 cells/mm³ or ANC greater than 20,000 cells/mm³: Interrupt LEUKINE treatment or reduce the dose by 50%

2.6 Acute Exposure to Myelosuppressive Doses of Radiation (H-ARS)

For patients with H-ARS, the recommended dose of LEUKINE is a subcutaneous injection administered once daily as follows:

- 7 mcg/kg in adult and pediatric patients weighing greater than 40 kg
- 10 mcg/kg in pediatric patients weighing 15 kg to 40 kg
- 12 mcg/kg in pediatric patients weighing less than 15 kg

Administer LEUKINE as soon as possible after suspected or confirmed exposure to radiation doses greater than 2 gray (Gy).

Estimate a patient's absorbed radiation dose (i.e., level of radiation exposure) based on information from public health authorities, biodosimetry if available, or clinical findings such as time to onset of vomiting or lymphocyte depletion kinetics.

Obtain a baseline CBC with differential and then serial CBCs approximately every third day until the ANC remains greater than 1,000/mm³ for three consecutive CBCs. Do not delay administration of LEUKINE if a CBC is not readily available.

Continue administration of LEUKINE until the ANC remains greater than 1,000/mm³ for three consecutive CBCs or exceeds 10,000/mm³ after a radiation-induced nadir.

2.7 Preparation and Administration of LEUKINE

- Do not administer LEUKINE simultaneously with or within 24 hours preceding cytotoxic chemotherapy or radiotherapy or within 24 hours following chemotherapy [*see Warnings and Precautions (5.3)*].
- LEUKINE injection is formulated as a sterile solution preserved with 1.1% benzyl alcohol.
- LEUKINE for injection is a sterile, preservative-free lyophilized powder that requires reconstitution with 1 mL Sterile Water for Injection (without preservative), USP, to yield a clear, colorless single-dose solution or 1 mL Bacteriostatic Water for Injection, USP (with 0.9% benzyl alcohol as preservative) to yield a clear, colorless single-dose solution.

Use only LEUKINE for injection (lyophilized powder) reconstituted with Sterile Water for Injection without preservatives when administering LEUKINE to neonates or infants to avoid benzyl alcohol exposure [*see Warnings and Precautions (5.9)*].

Do NOT use an in-line membrane filter for intravenous infusion of LEUKINE.

- Store LEUKINE solution and reconstituted lyophilized LEUKINE solutions under refrigeration at 2°C-8°C (36°F-46°F); DO NOT FREEZE.
- In the absence of compatibility and stability information, do not add other medication to infusion solutions containing LEUKINE. Use only 0.9% Sodium Chloride Injection, USP to prepare intravenous infusion solutions.
- 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.

LEUKINE for Injection (lyophilized powder) Preparation

Reconstitute LEUKINE for Injection aseptically with 1 mL of diluent. Do not mix the contents of vials reconstituted with different diluents together. Reconstitute with either Sterile Water for Injection, USP (without preservative) or Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol). Use reconstituted LEUKINE for injection (lyophilized powder) vials within 6 hours following reconstitution and/or dilution for intravenous infusion. Do not re-enter or reuse the vial. Discard any unused portions.

LEUKINE Injection (solution) Preparation

- For subcutaneous injection: Administer LEUKINE Injection without further dilution.
- For intravenous injection: Administer LEUKINE injection in 0.9% Sodium Chloride Injection, USP. Dilute LEUKINE for intravenous infusion in 0.9% Sodium Chloride Injection, USP. If the final concentration of LEUKINE is below 10 mcg/mL, add Albumin (Human) at a final concentration of 0.1% 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).

- Store LEUKINE injection for up to 20 days at 2°C-8°C once the vial has been entered. Discard any remaining solution after 20 days.

3 DOSAGE FORMS AND STRENGTHS

- For injection (lyophilized powder): 250 mcg of sargramostim, white powder in a single-dose vial for reconstitution
- Injection (solution): 500 mcg per mL clear, colorless solution of sargramostim in multiple-dose vials

4 CONTRAINDICATIONS

Do not administer LEUKINE to patients with a history of serious allergic reactions, including anaphylaxis, to human granulocyte-macrophage colony stimulating factor such as sargramostim, yeast-derived products, or any component of the product. Anaphylactic reactions have been reported with LEUKINE [see *Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylactic reactions, have been reported with LEUKINE. Parenteral administration of LEUKINE should be attended by appropriate precautions in case an allergic or untoward reaction occurs. If any serious allergic or anaphylactic reaction occurs, immediately discontinue LEUKINE therapy and institute medical management. Discontinue LEUKINE permanently for patients with serious allergic reactions.

5.2 Infusion Related Reactions

LEUKINE can cause infusion-related reactions. Infusion-related reactions may be characterized by respiratory distress, hypoxia, flushing, hypotension, syncope, and/or tachycardia 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.

Observe closely during infusion for symptoms, particularly in patients with pre-existing lung disease. If patients display dyspnea or other acute symptoms, reduce the rate of infusion by 50%. If symptoms persist or worsen despite rate reduction, discontinue the LEUKINE infusion. If patient experiences infusion-related reaction, subsequent intravenous infusions may be administered following the standard dose schedule with careful monitoring.

5.3 Risk of Severe Myelosuppression when LEUKINE Administered within 24 hours of Chemotherapy or Radiotherapy

Due to the potential sensitivity of rapidly dividing hematopoietic progenitor cells, LEUKINE should not be administered simultaneously with or within 24 hours preceding cytotoxic chemotherapy or radiotherapy or within 24 hours following chemotherapy. 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 reactions, including higher mortality and a higher incidence of grade 3 and 4 infections and grade 3 and 4 thrombocytopenia.

5.4 Effusions and Capillary Leak Syndrome

Edema, capillary leak syndrome, and 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/m²/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. Body weight and hydration status should be carefully monitored during LEUKINE administration.

5.5 Supraventricular Arrhythmias

Supraventricular arrhythmia has been reported in uncontrolled studies during LEUKINE administration, particularly in patients with a previous history of cardiac arrhythmia. These arrhythmias have been reversible after discontinuation of LEUKINE. Use LEUKINE with caution in patients with preexisting cardiac disease.

5.6 Leukocytosis

White blood cell counts of $\geq 50,000/\text{mm}^3$ were observed in patients receiving LEUKINE. Monitor complete blood counts (CBC) with differential twice per week. Base the decision whether to reduce the dose or interrupt treatment on the clinical condition of the patient [*see Dosage and Administration (2.1, 2.4, 2.5, 2.6)*]. Following cessation of LEUKINE therapy, excessive blood counts have returned to normal or baseline levels within 3 to 7 days.

5.7 Potential Effect on Malignant Cells

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.

Discontinue LEUKINE therapy if disease progression is detected during LEUKINE treatment.

5.8 Immunogenicity

Treatment with LEUKINE may induce neutralizing anti-drug antibodies. The incidence of anti-sargramostim neutralizing antibodies may be related to duration of exposure to LEUKINE. In a study of patients with normal neutrophil count and a solid tumor in complete response (an unapproved use) treated with LEUKINE for up to 12 months, 82.9% of 41 evaluable patients

developed anti-sargramostim neutralizing antibodies and the myelostimulatory effect of LEUKINE was not sustained by day 155 as assessed by WBC count. Use LEUKINE for the shortest duration required [*see Adverse Reactions (6.2)*].

5.9 Risk of Serious Adverse Reactions in Infants Due to Benzyl Alcohol Preservative

Serious and fatal adverse reactions including “gaspings syndrome” can occur in neonates and low birth weight infants treated with benzyl alcohol-preserved drugs, including LEUKINE injection (solution) or LEUKINE for injection (lyophilized powder) reconstituted with Bacteriostatic Water. The “gaspings syndrome” is characterized by central nervous system depression, metabolic acidosis and gasping respirations.

Avoid administration of solutions containing benzyl alcohol (including LEUKINE injection [solution] or LEUKINE for injection [lyophilized powder] reconstituted with Bacteriostatic Water for Injection, USP [0.9% benzyl alcohol]) to neonates and low birth weight infants. Instead, administer lyophilized LEUKINE reconstituted with Sterile Water for Injection, USP [*see Dosage and Administration (2.7)*].

If LEUKINE injection (solution) or LEUKINE for injection (lyophilized powder) reconstituted with Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol) must be used in neonates and low birth weight infants, consider the combined daily metabolic load of benzyl alcohol from all sources including LEUKINE (LEUKINE injection and LEUKINE for injection reconstituted with Bacteriostatic Water contain 11 mg and 9 mg of benzyl alcohol per mL, respectively). The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known [*see Use in Specific Populations (8.4) and Dosage and Administration (2.7)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Hypersensitivity Reactions [*see Warnings and Precautions (5.1)*]
- Infusion Related Reactions [*see Warnings and Precautions (5.2)*]
- Risk of Severe Myelosuppression when LEUKINE Administered within 24 Hours of Chemotherapy or Radiotherapy [*see Warnings and Precautions (5.3)*]
- Effusions and Capillary Leak Syndrome [*see Warnings and Precautions (5.4)*]
- Supraventricular Arrhythmias [*see Warnings and Precautions (5.5)*]
- Leukocytosis [*see Warnings and Precautions (5.6)*]
- Potential Effect on Malignant Cells [*see Warnings and Precautions (5.7)*]
- Immunogenicity [*see Warnings and Precautions (5.8)*]
- Risk of Serious Adverse Reactions in Infants Due to Benzyl Alcohol Preservative [*see Warnings and Precautions (5.9)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Autologous Peripheral Blood Progenitor Cell (PBPC) and Bone Marrow Transplantation

Studies 301, 302 and 303 enrolled a total of 156 patients after autologous or allogeneic marrow or PBPC transplantation. In these placebo-controlled studies, pediatric and adult patients received once-daily intravenous infusions of LEUKINE 250 mcg/m² or placebo for 21 days.

In Studies 301, 302, and 303, there was no difference in relapse rate between the LEUKINE and placebo-treated patients. Adverse reactions reported in at least 10% of patients who received intravenous LEUKINE or at a rate that was at least 5% higher than the placebo arm are shown in Table 1.

Table 1: Adverse Reactions after Autologous Marrow or PBPC Transplantation in at Least 10% of Patients Receiving Intravenous LEUKINE or at Least 5% Higher than the Placebo Arm

Adverse Reactions by Body System	LEUKINE (n=79) %	Placebo (n=77) %	Adverse Reactions 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			Blood and Lymphatic System		
Nausea	90	96	Blood dyscrasia	25	27
Diarrhea	89	82	Cardiovascular Vascular 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	Nervous System		
Stomatitis	24	29	CNS disorder	11	16
Liver damage	13	14			
Skin and Appendages					

Adverse Reactions by Body System	LEUKINE (n=79) %	Placebo (n=77) %	Adverse Reactions by Body System	LEUKINE (n=79) %	Placebo (n=77) %
Alopecia	73	74			
Rash	44	38			

Additional Clinically Significant Adverse Reactions Occurring in Less than 10% Incidence

Investigations: Elevated creatinine, elevated bilirubin, elevated transaminases

Allogeneic Bone Marrow Transplantation

In the placebo-controlled trial of 109 patients after allogeneic BMT (Study 9002), acute graft-vs-host disease occurred in 55% on the LEUKINE arm and in 59% on the placebo arm. Adverse reactions reported in at least 10% of patients who received IV LEUKINE or at a rate at least 5% higher than the placebo arm are shown in **Table 2**.

Table 2: Adverse Reactions after Allogeneic Marrow Transplantation in at Least 10% of Patients Receiving Intravenous LEUKINE or at Least 5% Higher than the Placebo Arm

Adverse Reactions by Body System	LEUKINE (n=53) %	Placebo (n=56) %	Adverse Reactions by Body System	LEUKINE (n=53) %	Placebo (n=56) %
Body, General			Eye hemorrhage	11	0
Fever	77	80	Cardiovascular System		
Abdominal pain	38	23	Hypertension	34	32
Headache	36	36	Tachycardia	11	9
Chills	25	20	Metabolic / Nutritional Disorders		
Pain	17	36	Bilirubinemia	30	27
Asthenia	17	20	Hyperglycemia	25	23
Chest pain	15	9	Peripheral edema	15	21
Digestive System			Increased creatinine	15	14
Diarrhea	81	66	Hypomagnesemia	15	9
Nausea	70	66	Increased SGPT	13	16
Vomiting	70	57	Edema	13	11
Stomatitis	62	63	Respiratory System		
Anorexia	51	57	Pharyngitis	23	13
Dyspepsia	17	20	Epistaxis	17	16

Adverse Reactions by Body System	LEUKINE (n=53) %	Placebo (n=56) %	Adverse Reactions by Body System	LEUKINE (n=53) %	Placebo (n=56) %
Hematemesis	13	7	Dyspnea	15	14
Dysphagia	11	7	Rhinitis	11	14
GI hemorrhage	11	5	Blood and Lymphatic System		
Skin and Appendages			Thrombocytopenia	19	34
Rash	70	73	Leukopenia	17	29
Alopecia	45	45	Nervous System		
Pruritus	23	13	Paresthesia	11	13
Musculoskeletal System			Insomnia	11	9
Bone pain	21	5	Anxiety	11	2
Arthralgia	11	4	Laboratory Abnormalities*		
Special Senses			High glucose	49	41
			Low albumin	36	27
			High BUN	17	23

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

Acute Myeloid Leukemia Following Induction Chemotherapy

Nearly all patients in both arms developed leukopenia, thrombocytopenia, and anemia. Adverse reactions reported in at least 10% of patients who received LEUKINE or at least 5% higher than the placebo arm are reported in Table 3.

Table 3: Adverse Reactions after Treatment of AML in at Least 10% of Patients Receiving Intravenous LEUKINE or at Least 5% Higher than the Placebo Arm

Adverse Reactions by Body System	LEUKINE (n=52) %	Placebo (n=47) %	Adverse Reactions by Body System	LEUKINE (n=52) %	Placebo (n=47) %
Body, General			Metabolic / Nutritional Disorder		
Fever (no infection)	81	74	Metabolic Laboratory Abnormalities	58	49
Infection	65	68	Edema	25	23

Adverse Reactions by Body System	LEUKINE (n=52) %	Placebo (n=47) %	Adverse Reactions by Body System	LEUKINE (n=52) %	Placebo (n=47) %
Weight loss	37	28	Respiratory System		
Chills	19	26	Pulmonary toxicity	48	64
Allergy	12	15	Blood and Lymphatic System		
Digestive System			Coagulation	19	21
Nausea	58	55	Cardiovascular System		
Liver toxicity	77	83	Hemorrhage	29	43
Diarrhea	52	53	Hypertension	25	32
Vomiting	46	34	Cardiac	23	32
Stomatitis	42	43	Hypotension	13	26
Anorexia	13	11	Urogenital System		
Skin and Appendages			GU abnormalities	50	57
Skin Reactions	77	45	Nervous System		
Alopecia	37	51	Neuro-clinical	42	53
			Neuro-motor	25	26
			Neuro-psych	15	26

There was no significant difference between the arms in the proportion of patients achieving complete remission (CR; 69% in the LEUKINE group and 55% in the placebo group). There was also 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 study was not sized to assess the impact of LEUKINE treatment on response.

Graft Failure

In a historically controlled study of 86 patients with 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). Headache (26%), pericardial effusion (25%), arthralgia (21%), and myalgia (18%) were also reported in patients treated with LEUKINE in the graft failure study.

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity with LEUKINE. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, duration of treatment, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to sargramostim in the studies described below with the incidence of antibodies in other studies or other products may be misleading.

In 214 patients with a variety of underlying diseases, neutralizing anti-sargramostim antibodies were detected in 5 patients (2.3%) after receiving LEUKINE by continuous IV infusion (3 patients) or SC injection (2 patients) for 28 to 84 days in multiple courses (as assessed by GM-CSF dependent human cell-line proliferation assay). All 5 patients had impaired hematopoiesis before the administration of LEUKINE, and consequently the effect of the development of anti-sargramostim antibodies on normal hematopoiesis could not be assessed.

Antibody studies of 75 patients with Crohn's disease (a disease for which LEUKINE is not indicated), with normal hematopoiesis and no other immunosuppressive drugs, receiving LEUKINE daily for 8 weeks by SC injection, showed 1 patient (1.3%) with detectable neutralizing anti-sargramostim antibodies (as assessed by GM-CSF dependent human cell-line proliferation assay).

In an experimental use trial where LEUKINE was given for an extended period, 53 patients with melanoma in complete remission (a disease for which LEUKINE is not indicated) received adjuvant therapy with LEUKINE 125 mcg/m² once daily (maximum dose 250 mcg) from day 1 to 14 every 28 days for 1 year. Serum samples from patients assessed at day 0, 2 weeks, 1 month, and 5 and/or 12 months were tested retrospectively for the presence of anti-sargramostim antibodies. Of 43 evaluable patients (having at least 3 timepoint samples post treatment), 42 (97.7%) developed anti-sargramostim binding antibody as assessed by ELISA and confirmed using an immunoprecipitation assay. Of these 42 patients, 41 had sufficient sample and were further tested: 34 patients (82.9%) developed anti-sargramostim neutralizing antibodies (as determined by a cell based luciferase reporter gene neutralizing antibody assay); 17 (50%) of these patients did not have a sustained pharmacodynamic effect of LEUKINE by day 155 as assessed by WBC counts. This study provided limited assessment of the impact of antibody formation on the safety and efficacy of LEUKINE.

Serious allergic and anaphylactoid reactions have been reported with LEUKINE, but the rate of occurrence of antibodies in such patients has not been assessed.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of LEUKINE in clinical trials and/or postmarketing surveillance. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Infusion related reactions including dyspnea, hypoxia, flushing, hypotension, syncope and/or tachycardia [*see Warnings and Precautions (5.1)*]

- Serious allergic reactions/hypersensitivity, including anaphylaxis, skin rash, urticaria, generalized erythema, and flushing [*see Warnings and Precautions (5.2)*]
- Effusions and capillary leak syndrome [*see Warnings and Precautions (5.3)*]
- Supraventricular arrhythmias [*see Warnings and Precautions (5.4)*]
- Leukocytosis including eosinophilia [*see Warnings and Precautions (5.6)*]
- Thromboembolic events
- Pain, including chest, abdominal, back, and joint pain
- Injection site reactions

7 DRUG INTERACTIONS

7.1 Concomitant Use with Products that Induce Myeloproliferation

Avoid the concomitant use of LEUKINE and products that induce myeloproliferation (such as lithium and corticosteroids). Such products may increase the myeloproliferative effects of LEUKINE. Monitor patients receiving both LEUKINE and products that induce myeloproliferation frequently for clinical and laboratory signs of excess myeloproliferative effects.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Both LEUKINE injection (solution) and LEUKINE for injection (lyophilized powder) reconstituted with Bacteriostatic Water for Injection, USP contain benzyl alcohol, which has been associated with gasping syndrome in neonates and infants. The preservative benzyl alcohol can cause serious adverse reactions and death when administered intravenously to neonates and infants. If LEUKINE is needed during pregnancy, use only LEUKINE for injection (lyophilized powder) reconstituted with Sterile Water for injection without preservatives [*see Dosage and Administration (2.7) and Use in Specific Populations (8.4)*].

The limited available data on LEUKINE use in pregnant women are insufficient to inform the drug-associated risk of adverse developmental outcomes. Based on animal studies LEUKINE may cause embryofetal harm. In animal reproduction studies, administration of LEUKINE to pregnant rabbits during organogenesis resulted in adverse developmental outcomes including increased spontaneous abortion at systemic exposures ≥ 1.3 times the human exposure expected at the recommended human dose [*see Data*]. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2%-4% and 15%-20%, respectively.

Data

Animal data

In an embryofetal developmental study and a prenatal and postnatal study, pregnant rabbits were administered SC doses of LEUKINE during the period of gestation day (GD) 6 to GD19, GD19 to GD28, or GD19 to parturition at 25, 70, and 200 mcg/kg/day. An increase in spontaneous abortions, late resorptions, and postimplantation loss, and a reduction in viable fetuses, mean live litter size, and offspring body weight were evident in rabbits treated with LEUKINE at 200 mcg/kg/day. No adverse effects were observed at ≤ 70 mcg/kg/day.

After the first administration in rabbits, the dose of 200 mcg/kg/day corresponds to a systemic exposure (AUC) of approximately 11-25.3 times the exposures observed in patients treated with the clinical LEUKINE dose of 250 mcg/m²; however, due to the production of anti-LEUKINE antibodies with repeat administration, the AUC in rabbits was reduced to 1.3-5.5 times the clinical exposure by the end of the dosing periods.

Similarly, after the first administration in rabbits, the dose of 70 mcg/kg/day corresponds to a systemic exposure (AUC) of approximately 7 to 11 times the exposures observed in patients treated with the clinical LEUKINE dose of 250 mcg/m²; however, due to the production of anti-LEUKINE antibodies with repeat administration, the AUC in rabbits was reduced to 1.0-1.2 times the clinical exposure by the end of the dosing periods.

8.2 Lactation

Risk Summary

There is no information regarding the presence of LEUKINE in human milk, the effects on the breastfed child, or the effects on milk production. Administration of LEUKINE to rabbits during lactation resulted in reduction in postnatal offspring survival [*see Data*]. Because of the potential for serious adverse reactions advise a lactating woman not to breastfeed during treatment and for at least 2 weeks after the last dose.

Data

There are no data regarding the presence of LEUKINE in rabbit milk. However, in the prenatal and postnatal study, lactating rabbits were administered SC doses of LEUKINE during the period of lactation day (LD) 1 to LD14 at 25, 70, and 200 mcg/kg/day. At doses ≥ 25 mcg/kg/day a reduction in postnatal offspring survival was observed. Maternal toxicity was also observed at LEUKINE doses ≥ 25 mcg/kg/day.

After the first administration in rabbits, the dose of 25 mcg/kg/day corresponds to a systemic AUC of approximately 2.6 times the exposure observed in patients treated with the clinical LEUKINE dose of 250 mcg/m² however, due to the production of anti-LEUKINE antibodies with repeat administration, the exposure in rabbits decreased to 0.2 times the clinical exposure by the end of the dosing period.

8.4 Pediatric Use

The safety and effectiveness of LEUKINE have been established in pediatric patients 2 years of age and older for autologous peripheral blood progenitor cells and bone marrow transplantation, allogeneic bone marrow transplantation, and treatment of delayed neutrophil recovery or graft failure. Use of LEUKINE for these indications in this age group is based on adequate and well-controlled studies of LEUKINE in adults, in addition to clinical data in 12, 23, and 37 pediatric

patients, respectively [See *Clinical Studies (14.3, 14.4 and 14.5)*]. The pediatric adverse reactions were consistent with those reported in the adult population.

The safety and effectiveness of LEUKINE for pediatric patients less than 2 years of age for autologous peripheral blood progenitor cells and bone marrow transplantation, allogeneic bone marrow transplantation, and treatment of delayed neutrophil recovery or graft failure have not been established.

The use of LEUKINE to increase survival in pediatric patients acutely exposed to myelosuppressive doses of radiation (H-ARS) is based on efficacy studies conducted in animals and clinical data supporting the use of LEUKINE in patients undergoing autologous or allogeneic BMT following myelosuppressive chemotherapy with or without total body irradiation. Efficacy studies of LEUKINE could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Modeling and simulation was used to derive dosing regimens that are predicted to provide pediatric patients with exposure comparable to the observed exposure in adults receiving 7 mcg/kg [see *Clinical Pharmacology (12.3)*]. The dose for pediatric patients is based on weight [see *Dosage and Administration (2.2)*].

Safety and effectiveness in pediatric patients have not been established in:

- Acute Myeloid Leukemia: Neutrophil Recovery Following Induction Chemotherapy
- Autologous Peripheral Blood Progenitor Cell Mobilization and Collection

Avoid administration of solutions containing benzyl alcohol [including LEUKINE injection (solution) or LEUKINE for injection (lyophilized powder) reconstituted with Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol)] to neonates and low birth weight infants. Instead, administer lyophilized LEUKINE reconstituted with Sterile Water for Injection, USP [see *Dosage and Administration (2.7)*].

Serious adverse reactions including fatal reactions and the “gaspings syndrome” occurred in premature infants in the neonatal intensive care unit who received drugs containing benzyl alcohol as a preservative. In these cases, benzyl alcohol dosages of 99 to 234 mg/kg/day produced high levels of benzyl alcohol and its metabolites in the blood and urine (blood levels of benzyl alcohol were 0.61 to 1.38 mmol/L). Additional adverse reactions included gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Preterm, low birth weight infants may be more likely to develop these reactions because they may be less able to metabolize benzyl alcohol.

If LEUKINE injection (solution) or LEUKINE for injection (lyophilized powder) reconstituted with Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol) must be used in neonates and low birth weight infants, consider the combined daily metabolic load of benzyl alcohol from all sources including LEUKINE (LEUKINE injection [solution] and LEUKINE for injection [lyophilized powder] reconstituted with Bacteriostatic Water for Injection, USP [0.9% benzyl alcohol] contain 11 mg and 9 mg of benzyl alcohol per mL, respectively). The minimum amount

of benzyl alcohol at which serious adverse reactions may occur is not known [see *Dosage and Administration* (2.7)].

8.5 Geriatric Use

Clinical studies of LEUKINE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

10 OVERDOSAGE

Doses up to 100 mcg/kg/day (4,000 mcg/m²/day or 16 times the recommended dose) were administered to four patients in a Phase 1 uncontrolled clinical study by continuous IV infusion for 7 to 18 days. Increases in WBC up to 200,000 cells/mm³ 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, discontinue LEUKINE therapy and monitor the patient for WBC increase and respiratory symptoms.

11 DESCRIPTION

LEUKINE (sargramostim) injection and LEUKINE (sargramostim) for injection for subcutaneous or intravenous use are recombinant human granulocyte-macrophage colony stimulating factor (rhu GM-CSF) produced by recombinant DNA technology in a yeast (*S. cerevisiae*) expression system. 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. LEUKINE differs from human GM-CSF by one amino acid at position 23, where leucine is substituted for arginine.

LEUKINE (sargramostim) injection is a sterile, clear, colorless solution preserved with 1.1% benzyl alcohol in a multiple-dose vial. Each 1 mL vial contains 500 mcg sargramostim and has a pH range of 6.7 - 7.7. LEUKINE (sargramostim) for injection is supplied as a sterile, preservative-free, white lyophilized powder in a single-dose vial. Each single-dose vial delivers 250 mcg sargramostim. Inactive ingredients are mannitol (40 mg), sucrose (10 mg), and tromethamine (1.2 mg). Reconstitution with 1 mL of the appropriate diluent (sterile water for injection or bacteriostatic water for injection) yields a solution containing 250 mcg/mL sargramostim at a pH range of 7.1 - 7.7 with a deliverable volume of 1 mL (250 mcg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sargramostim (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. 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.

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 GM-CSF. *In vitro* exposure of human bone marrow cells to GM-CSF 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 granulocyte macrophage colonies. Chemotactic, anti-fungal, and anti-parasitic activities of granulocytes and monocytes are increased by exposure to GM-CSF *in vitro*. GM-CSF increases the cytotoxicity of monocytes toward certain neoplastic cell lines and activates polymorphonuclear neutrophils to inhibit the growth of tumor cells.

12.2 Pharmacodynamics

LEUKINE stimulates hematopoietic precursor cells and increases neutrophil, eosinophil, megakaryocyte, macrophage, and dendritic cell production. In AML adult patients undergoing induction chemotherapy [see *Clinical Studies (14.1)*], LEUKINE at daily doses of 250 mcg/m² significantly shortened the median duration of ANC <500/mm³ by 4 days and <1000/mm³ by 7 days following induction; 75% of patients receiving sargramostim achieved ANC greater than 500/mm³ by day 16 compared to day 25 for patients receiving placebo. Animal data and clinical data in humans suggest a correlation between sargramostim exposure and the duration of severe neutropenia as a predictor of efficacy. At doses of 250 mcg/m² (approximately 7 mcg/kg in a 70 kg human with a body surface area of 1.96), daily LEUKINE treatment reduced the duration of severe neutropenia.

12.3 Pharmacokinetics

Intravenous Administration (IV)

Peak concentrations of sargramostim were observed in blood samples obtained during or immediately after completion of LEUKINE infusion. For LEUKINE injection, the mean maximum concentration (C_{max}) was 16.7 ng/mL and the mean area under the time-concentration curve (AUC)_{0-inf} was 32.9 ng•h /mL. There is no accumulation of GM-CSF after repeat dosing and steady state conditions are met after a single dose.

Subcutaneous Administration (SC)

LEUKINE injection and LEUKINE for injection, at a dose of 6.5 mcg/kg (approximately 250 mcg/m²) given by the SC route, have been determined to be bioequivalent. Based on a population pharmacokinetics analysis of lyophilized LEUKINE data, the mean C_{max} after a 7 mcg/kg SC dose (equivalent to a 250 mcg/m² dose in a 70 kg human with a body surface area of 1.96) was 3.03 ng/mL and mean AUC₀₋₂₄ was 21.3 ng•h/mL (Table 4). There is no accumulation of GM-CSF after repeat SC dosing and steady state conditions are met after a single SC dose.

Table 4: Sargramostim serum C_{max} and AUC Exposure (CV%) in Humans after Subcutaneous Administration

Data type	Sargramostim dose	Formulation	Number of healthy subjects	AUC (CV%) (ng·h/mL)	C _{max} (CV%) (ng/mL)
Observed	250 mcg/m ² ^a	LEUKINE injection	29 29	21.9 (28.1%) 20.3 (32.4%)	3.75 (45.5%) 3.24 (50.5%)
Observed	6.5 mcg/kg	Lyophilized LEUKINE	39	20.4 (28.7%)	3.15 (35.2%)
Population PK model simulation	7 mcg/kg	Lyophilized LEUKINE	500	21.3 (32.6)	3.03 (31.0)

^a 250 mcg/m² is approximately 7 mcg/kg in 70 kg patient with a body surface area of 1.96 M²

Absorption

After SC administration GM-CSF was detected in the serum early (15 min) and reached maximum serum concentrations between 2.5 and 4 h. The absolute bioavailability with the SC route, when compared to the IV route, was 75%.

Distribution

The observed volume of distribution after IV (V_z) administration was 96.8.

Elimination

When a 500 mcg dose of LEUKINE (injection) was administered IV over two hours to healthy volunteers, the mean terminal elimination half-life was approximately 3.84 h and the mean clearance rate was approximately 17.2 L/h. When LEUKINE (lyophilized product) was administered SC to healthy adult volunteers, GM-CSF and had a terminal elimination half-life of 1.4 h. The observed total body clearance/subcutaneous bioavailability (CL/F) was 23 L/h. Specific metabolism studies were not conducted, because LEUKINE is a protein and is expected to degrade to small peptides and individual amino acids.

Special Populations

Adult patients acutely exposed to myelosuppressive doses of radiation (H-ARS)

The pharmacokinetics of sargramostim are not available in adult patients acutely exposed to myelosuppressive doses of radiation. Pharmacokinetic data in irradiated and non-irradiated non-human primates and in healthy human adults were used to derive human doses for patients acutely exposed to myelosuppressive doses of radiation. Modeling and simulation of the healthy human adult pharmacokinetic data indicate that sargramostim C_{max} and AUC exposures at a LEUKINE dose of 7 mcg/kg in patients acutely exposed to myelosuppressive doses of radiation are expected to exceed sargramostim C_{max} (97.6% of patients) and AUC (100% of patients) exposures at a LEUKINE dose of 7 mcg/kg in non-human primates.

Pediatric patients acutely exposed to myelosuppressive doses of radiation (H-ARS)

The pharmacokinetics of sargramostim was not available in pediatric patients acutely exposed to myelosuppressive doses of radiation. The pharmacokinetics of sargramostim in pediatric patients after being exposed to myelosuppressive doses of radiation were estimated by scaling the adult population pharmacokinetic model to the pediatric population. The model-predicted mean AUC₀₋₂₄ values at 7, 10, and 12 mcg/kg doses of LEUKINE in pediatric patients weighing greater than

40 kg (~adolescents), 15 to 40 kg (~young children), and 0 to less than 15 kg (~newborns to toddlers), respectively, were similar to AUC values in adults after a 7 mcg/kg dose.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Carcinogenicity and genetic toxicology studies have not been conducted with LEUKINE.

Impairment of Fertility

LEUKINE had no effect on fertility of female rabbits up to a dose of 200 mcg/kg/day.

The toxicology studies with up to 6 weeks of exposure to LEUKINE in sexually mature female and male cynomolgus monkeys did not reveal findings in male or female reproductive organs that would suggest impairment of fertility up to a dose of 200 mcg/kg/day. At 200 mcg/kg, the AUC exposure of LEUKINE was 8.8 to 11.4 times (monkeys) and 2.0 to 25.3 times (rabbits) the exposure in humans at the recommended clinical dose of 250 mcg/m².

After the first administration, a dose of 200 mcg/kg/day corresponds to an AUC of approximately 11.4 (monkeys) and 25.3 (rabbits) times the exposures observed in patients treated with the clinical LEUKINE dose of 250 mcg/m²; however, due to the production of anti-LEUKINE antibodies with repeat administration, the AUC decreased to 8.8 (monkeys) and 2.0 (rabbits) times the clinical exposure by the end of the dosing periods.

14 CLINICAL STUDIES

14.1 Following Induction Chemotherapy for Acute Myelogenous Leukemia

The efficacy of LEUKINE in the treatment of AML was evaluated in a multicenter, randomized, double-blind placebo-controlled trial (study 305) of 99 newly-diagnosed adult patients, 55-70 years of age, receiving induction with or without consolidation. 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/m²/day) or placebo was given intravenously over four hours each day, starting four days after the completion of chemotherapy. Study drug was continued until an ANC \geq 1500 cells/mm³ 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 cells/mm³ by 4 days and <1000 cells/mm³ by 7 days following induction (see Table 5). Of patients receiving LEUKINE, 75% achieved ANC >500 cells/mm³ 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 vs. 15 days) or two cycles (14 vs. 23 days) of induction chemotherapy was administered. Median times to platelet ($>20,000$ cells/mm³) and RBC transfusion independence were not significantly different between treatment groups.

Table 5: Hematological Recovery (in Days) in Patients with AML: Induction

Dataset	LEUKINE n=52 ^a Median (25%, 75%)	Placebo n=47 Median (25%, 75%)	p-value ^b
ANC >500 /mm ³ ^c	13 (11, 16)	17 (13, 25)	0.009
ANC >1000 /mm ³ ^d	14 (12, 18)	21 (13, 34)	0.003
PLT $>20,000$ /mm ³ ^e	11 (7, 14)	12 (9, >42)	0.10
RBC ^f	12 (9, 24)	14 (9, 42)	0.53

^a Patients with missing data censored

^b p = Generalized Wilcoxon

^c 2 patients on LEUKINE and 4 patients on placebo had missing values

^d 2 patients on LEUKINE and 3 patients on placebo had missing values

^e 4 patients on placebo had missing values

^f 3 patients on LEUKINE 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 cells/mm³ (13 days) or 1000 cells/mm³ (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 vs. 11, p=0.02). The majority of deaths in the placebo group were associated with fungal infections with pneumonia as the primary infection.

14.2 Autologous Peripheral Blood Progenitor Cell Mobilization and Collection

A retrospective review was conducted of data from adult 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/m²/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 cells/mm³. Leukaphereses continued until both a minimum number of mononucleated cells (MNC) were collected (6.5 or 8.0×10^8 /kg body weight) and a minimum number of aphereses (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/mm³ by day 5, another cytokine was substituted for LEUKINE.

Marked mobilization effects were seen in patients administered the higher dose of LEUKINE (250 mcg/m²) either IV (n=63) or SC (n=41). PBPCs from patients treated at the 250 mcg/m²/day dose had a significantly higher number of granulocyte-macrophage colony-forming units (CFU-GM) than those collected without mobilization. The mean value after thawing was 11.41 × 10⁴ CFU-GM/kg for all LEUKINE-mobilized patients, compared to 0.96 × 10⁴/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 × 10⁴/kg for patients mobilized with 250 mcg/m² doses of LEUKINE administered SC vs. 1.63 × 10⁴/kg for non-mobilized patients).

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/m²/day once a day (n=10) or twice a day (n=21) until completion of apheresis. Apheresis was begun on day 5 of LEUKINE administration and continued until the targeted MNC count of 9 × 10⁸/kg or CD34+ cell count of 1 × 10⁶/kg was reached. There was no difference in CD34+ cell count in patients receiving LEUKINE once or twice a day.

14.3 Autologous Peripheral Blood Progenitor Cell and Bone Marrow Transplantation

The efficacy of LEUKINE to accelerate myeloid reconstitution following autologous PBPC was established in the retrospective review above. After transplantation, mobilized subjects had shorter times to neutrophil recovery and fewer days between transplantation and the last platelet transfusion compared to non-mobilized subjects. Neutrophil recovery (ANC >500 cells/mm³) was more rapid in patients administered LEUKINE following PBPC transplantation with LEUKINE-mobilized cells (see Table 6). 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 6: ANC and Platelet Recovery after PBPC Transplantation

	LEUKINE Route for Mobilization	Post transplant LEUKINE	Median Day ANC >500 cells/mm³	Median Day of 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

The efficacy of LEUKINE on time to myeloid reconstitution following autologous BMT was established by three single-center, randomized, placebo-controlled and double-blinded studies (studies 301, 302, and 303) in adult and pediatric patients undergoing autologous BMT for lymphoid malignancies. A total of 128 patients (65 LEUKINE, 63 placebo) were enrolled in these three studies. The median age was 38 years (range 3-62 years), and 12 patients were younger than 18 years of age. The majority of the patients had lymphoid malignancy (87 NHL, 17 ALL), 23 patients had Hodgkin lymphoma, and one patient had AML. In 72 patients with

NHL or ALL, the bone marrow harvest was purged with one of several monoclonal antibodies prior to storage. 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/m²) and carmustine (300 mg/m²), cyclophosphamide (140-150 mg/kg), hydroxyurea (4.5 grams/m²), and etoposide (375-450 mg/m²).

Compared to placebo, administration of LEUKINE in two studies (study 301: 44 patients, 23 patients treated with LEUKINE, and study 303: 47 patients, 24 treated with LEUKINE) significantly improved the following hematologic and clinical endpoints: time to neutrophil recovery, duration of hospitalization and infection experience or antibacterial usage. In the third study (study 302: 37 patients who underwent autologous BMT, 18 treated with LEUKINE) 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 lymphoma who had also received extensive radiation and chemotherapy prior to harvest of autologous bone marrow. In the following combined analysis of the three studies, these two subgroups (NHL and ALL vs. Hodgkin lymphoma) are presented separately.

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

Neutrophil recovery (ANC ≥500 cells/mm³) in 54 patients with NHL or ALL receiving LEUKINE on Studies 301, 302 and 303 was observed on day 18, and on day 24 in 50 patients treated with placebo (see Table 7). 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.

Table 7: Autologous BMT: Combined Analysis from Placebo-Controlled Clinical Trials of Responses in Patients with NHL and ALL Median Values (days)

	ANC ≥500 cells /mm ³	ANC ≥1000 cells/mm ³	Duration of Hospitalization	Duration of Infection	Duration of Antibacterial Therapy
LEUKINE n=54	18 ^{a,b}	24 ^{a, b}	25 ^a	1 ^a	21 ^a
Placebo n=50	24	32	31	4	25

^a p <0.05 Wilcoxon or Cochran-Mantel-Haenszel RIDIT chi-squared

^b p <0.05 Log rank

14.4 Allogeneic Bone Marrow Transplantation

A multicenter, randomized, placebo-controlled, and double-blinded study (study 9002) was conducted to evaluate the safety and efficacy of LEUKINE for promoting hematopoietic reconstitution following allogeneic BMT. A total of 109 adult and pediatric patients (53 LEUKINE, 56 placebo) were enrolled in the study. The median age was 34.7 years (range 2.2-65.1 years). 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 GVHD prophylaxis was cyclosporine 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 8).

Table 8: 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 ^a	14 ^a	30 ^a	9 ^b	25 ^a
Placebo n=56	17	19	42	19	26

^a p <0.05 generalized Wilcoxon test

^b p <0.05 simple chi-square test

Median time to myeloid recovery (ANC ≥500 cells/mm³) in 53 patients receiving LEUKINE was 4 four days less than in 56 patients treated with placebo (see Table 8). The numbers of patients with bacteremia and infection were 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 a shorter median number of days to last platelet and RBC transfusions compared to placebo patients, but none of these differences reached statistical significance.

14.5 Treatment of Delayed Neutrophil Recovery or Graft Failure After Allogeneic or Autologous Bone Marrow Transplantation

A historically-controlled study (study 501) 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 neutrophil recovery ($ANC \leq 100$ cells/mm³ by day 28 post transplantation);
2. patients displaying a delay in neutrophil recovery ($ANC \leq 100$ cells/mm³ by day 21 post transplantation) and who had evidence of an active infection; and
3. patients who lost their marrow graft after a transient neutrophil recovery (manifested by an average of $ANC \geq 500$ cells/mm³ for at least one week followed by loss of engraftment with $ANC < 500$ cells/mm³ for at least one week beyond day 21 post transplantation).

A total of 140 eligible adult and pediatric 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 NHL, 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. The median age of enrolled patients was 27 years (range 1-66 years). Thirty-seven patients were younger than 18 years of age.

One hundred-day survival was improved in favor of the patients treated with LEUKINE for 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 Multiple Organ Failure (MOF) score is a clinical and laboratory assessment of seven major organ systems: cardiovascular, respiratory, gastrointestinal, hematologic, renal, hepatic and neurologic. Median survival by MOF category is presented in Table 9.

Table 9: 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)

14.6 Acute Exposure to Myelosuppressive Doses of Radiation (H-ARS)

Efficacy studies of LEUKINE could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. The use of LEUKINE in the H-ARS indication was based on efficacy studies conducted in animals and data supporting LEUKINE's effect on severe neutropenia in patients undergoing autologous or allogeneic BMT following myelosuppressive chemotherapy with or without total body irradiation, and in patients with acute myelogenous leukemia following myelosuppressive chemotherapy [see *Dosage and Administration (2.1 to 2.6)*].

The recommended dose of LEUKINE for adults exposed to myelosuppressive doses of radiation is 7 mcg/kg as a single daily SC injection [see *Dosage and Administration (2.6)*]. The 7 mcg/kg dosing regimen is based on population modeling and simulation analyses. The sargramostim exposure associated with the 7 mcg/kg adult dose is expected to be higher than sargramostim exposure in the nonclinical efficacy study and therefore are expected to provide sufficient pharmacodynamic activity to treat humans exposed to myelosuppressive doses of radiation [see *Clinical Pharmacology (12.3)*]. The safety of LEUKINE at a dose of 250 mcg/m²/day (approximately 7 mcg/kg) has been assessed on the basis of clinical experience in myeloid reconstitution in patients after autologous or allogeneic BMT, and in patients with AML [see *Adverse Reactions (6.1)*].

The efficacy of LEUKINE was studied in a randomized, blinded, placebo-controlled study in a nonhuman primate model of radiation injury. Rhesus macaques (50% male) were randomized to a control (n = 36) or treated (n = 36) group. Animals were exposed to total body irradiation at a dose that would be lethal in 50% to 60% of animals (655 cGy) by day 60 post irradiation (lethal dose [LD]_{50-60/60}). Starting 48 ± 1 hour after irradiation, animals received daily SC injections of placebo (sterile water for injection, USP) or LEUKINE (7 mcg/kg/day). Blinded treatment was stopped when one of the following criteria was met: ANC ≥1,000 cells/mm³ for 3 consecutive days or if the ANC ≥10,000 cells/mm³. Animals received minimal supportive care that included a prophylactic antibiotic, antiemetic, analgesics and parenteral fluids. No whole blood, blood products or individualized antibiotics were provided.

LEUKINE significantly (p=0.0018) increased survival at day 60 in irradiated nonhuman primates: 78% survival (28/36) in the LEUKINE group compared to 42% survival (15/36) in the control group.

In the same study, an exploratory cohort of 36 rhesus macaques randomized to control (n=18) or treated (n=18) was exposed to total body irradiation at a dose that would be lethal in 70-80% of animals (713 cGY) by day 60 post irradiation. LEUKINE increased survival at day 60 in irradiated nonhuman primates: 61% survival (11/18) in the LEUKINE group compared to 17% survival (3/18) in the control group.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

LEUKINE (sargramostim) for injection is a sterile, preservative-free, white lyophilized powder supplied in a carton containing five 250 mcg single-dose vials. (NDC 71837-5843-5).

LEUKINE (sargramostim) injection is a sterile, clear, colorless solution preserved with 1.1% benzyl alcohol supplied in a carton containing one 500 mcg/mL multiple-dose vial (NDC 71837-

5844-1) and a carton containing five 500 mcg/mL multiple-dose vials (NDC 71837-5844-5).

Storage and Handling

Store LEUKINE vials refrigerated at 2°C-8°C (36°F-46°F) in the original carton to protect from light. Do not freeze or shake. Do not use beyond the expiration date printed on the vial.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

LEUKINE should be used under the guidance and supervision of a health care professional. However, if 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 (2.7)*]. 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.

Advise patients of the following risks and potential risks with LEUKINE:

- Serious allergic reactions [*see Warnings and Precautions (5.1)*]
- Infusion related reactions [*see Warnings and Precautions (5.2)*]
- Risk of severe myelosuppression when LEUKINE administered within 24 hours of chemotherapy or radiotherapy [*see Warnings and Precautions (5.3)*]
- Effusions and capillary leak syndrome [*see Warnings and Precautions (5.4)*]
- Supraventricular arrhythmias [*see Warnings and Precautions (5.5)*]
- Leukocytosis including eosinophilia [*see Warnings and Precautions (5.6)*]
- Potential effect on malignant cells [*see Warnings and Precautions (5.7)*]
- Pain including chest, abdominal, back, and joint pain [*see Adverse Reactions (6.1)*]
- Thromboembolic events [*see Adverse Reactions (6.3)*]
- Embryofetal Toxicity: Advise females of reproductive potential that LEUKINE may cause fetal harm and to inform their prescriber of a known or suspected pregnancy [*see Use in Specific Populations (8.1)*]
- Lactation: Advise lactating woman not to breastfeed during treatment and for at least 2 weeks after the last dose [*see Use in Specific Populations (8.2)*]
- Advise patients acutely exposed to myelosuppressive doses of radiation (H-ARS) that efficacy studies of LEUKINE for this indication could not be conducted in humans for ethical and feasibility reasons and that, therefore, approval of this use was based on efficacy studies conducted in animals [*see Clinical Studies (14.6)*]

Instruct patients who self-administer LEUKINE:

- Follow the Instructions for Use

- Do not reuse needles, syringes, or unused portions of vials
- Follow local requirements for proper disposal of used syringes, needles, and unused vials

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