Steps for the preparation of LEUKINE (sargramostim)

1. Liquid LEUKINE® is formulated as a sterile, preserved (1.1% benzyl alcohol), injectable solution (500 mcg/mL) in a vial. Lyophilized LEUKINE is a sterile, white, preservative-free powder (250 mcg) that requires reconstitution with 1 mL Sterile Water for Injection, USP, or 1 mL Bacteriostatic Water for Injection, USP.

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

3. Lyophilized LEUKINE (250 mcg) should be reconstituted aseptically with 1.0 mL of diluent (see below). The contents of vials reconstituted with different diluents should not be mixed together.

   Sterile Water for Injection, USP (without preservative): Lyophilized LEUKINE vials contain no antibacterial preservative, and therefore solutions prepared with Sterile Water for Injection, USP should be administered as soon as possible, and within 6 hours following reconstitution and/or dilution for IV infusion. The vial should not be re-entered or reused. Do not save any unused portion for administration more than 6 hours following reconstitution.

   Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol): Reconstituted solutions prepared with Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol) may be stored for up to 20 days at 2-8°C prior to use. Discard reconstituted solution after 20 days. Previously reconstituted solutions mixed with freshly reconstituted solutions must be administered within 6 hours following mixing.

Preparations containing benzyl alcohol (including liquid LEUKINE and lyophilized LEUKINE reconstituted with Bacteriostatic Water for Injection) should not be used in neonates (see WARNINGS in the enclosed full Prescribing Information).

Indication

LEUKINE is indicated for the following uses: (i) following induction chemotherapy in older adult patients with acute myelogenous leukemia (AML) to shorten time to neutrophil recovery; (ii) for mobilization and following transplantation of autologous peripheral blood progenitor cells; (iii) for myeloid reconstitution after autologous or allogeneic bone marrow transplantation (BMT); (iv) for use in bone marrow transplantation failure or engraftment delay.

Important Safety Information for Leukine® (sargramostim)

- Leukine is contraindicated in patients with excessive leukemic myeloid blasts in bone marrow or peripheral blood (≥10%); in patients with known hypersensitivity to GM-CSF, yeast-derived products, or any component of Leukine; and for concomitant use with chemotherapy and radiotherapy.

Please see additional Important Safety Information on following pages and full Prescribing Information available at www.leukine.com.
4. During reconstitution of lyophilized LEUKINE the diluent should be directed at the side of the vial and the contents gently swirled to avoid foaming during dissolution. Avoid excessive or vigorous agitation; do not shake.

5. LEUKINE should be used for SC injection without further dilution. Dilution for IV infusion should be performed in 0.9% Sodium Chloride Injection, USP. If the final concentration of LEUKINE is below 10 mcg/mL, Albumin (Human) at a final concentration of 0.1% should be added to the saline prior to addition of LEUKINE to prevent adsorption to the components of the drug delivery system. To obtain a final concentration of 0.1% Albumin (Human), add 1 mg Albumin (Human) per 1 mL 0.9% Sodium Chloride Injection, USP (eg, use 1 mL 5% Albumin [Human] in 50 mL 0.9% Sodium Chloride Injection, USP).

**Important Safety Information for Leukine® (sargramostim)**

- Serious allergic or anaphylactic reactions have been reported with Leukine. If any serious allergic or anaphylactic reactions occur, Leukine therapy should be immediately discontinued and appropriate therapy initiated.

- Liquid solutions containing benzyl alcohol (including liquid Leukine) or lyophilized Leukine reconstituted with Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol) should not be administered to neonates.

- Leukine should be used with caution and monitored in patients with preexisting fluid retention, pulmonary infiltrates, or congestive heart failure, respiratory symptoms or disease; cardiac symptoms or disease; and renal or hepatic dysfunction.

- Edema, capillary leak syndrome, pleural and/or pericardial effusion, sequestration of granulocytes in the pulmonary circulation, and dyspnea have been reported in patients after Leukine administration. Occasional transient supraventricular arrhythmia has been reported during Leukine administration. Leukine has induced the elevation of serum creatinine or bilirubin and hepatic enzymes in some patients. Monitoring of renal and hepatic function in patients with preexisting renal or hepatic dysfunction is recommended at least every other week during Leukine administration.

Please see additional Important Safety Information on previous and following page and full Prescribing Information available at [www.leukine.com](http://www.leukine.com).
6. An in-line membrane filter should NOT be used for IV infusion of LEUKINE.

7. Store liquid LEUKINE® and reconstituted lyophilized LEUKINE solutions under refrigeration at 2-8°C (36-46°F); DO NOT FREEZE.

8. In the absence of compatibility and stability information, no other medication should be added to infusion solutions containing LEUKINE. Use only 0.9% Sodium Chloride Injection, USP to prepare IV infusion solutions.

9. Aseptic technique should be employed in the preparation of all LEUKINE solutions. To assure correct concentration following reconstitution, care should be exercised to eliminate any air bubbles from the needle hub of the syringe used to prepare the diluent. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter is present or the solution is discolored, the vial should not be used.

Important Safety Information for Leukine® (sargramostim)

• Adverse events occurring in >10% of patients receiving Leukine in controlled clinical trials and reported in a higher frequency than placebo were: in AML patients – (fever, skin reactions, metabolic disturbances, nausea, vomiting, weight-loss, edema, anorexia); in Autologous BMT patients – (asthenia, malaise, diarrhea, rash, peripheral edema, urinary tract disorder); and in Allogeneic BMT patients – (abdominal pain, chills, chest pain, diarrhea, nausea, vomiting, hematemesis, dysphagia, GI hemorrhage, pruritus, bone pain, arthralgia, eye hemorrhage, hypertension, tachycardia, bilirubinemia, hyperglycemia, increased creatinine, hypomagnesemia, edema, pharyngitis, epistaxis, dyspnea, insomnia, anxiety, high BUN, and high cholesterol).

• If ANC > 20,000 cells/mm³ or if platelet counts > 500,000/mm³, Leukine administration should be interrupted or the dose reduced by half. Twice weekly monitoring of CBC with differential should be performed.

• Leukine therapy should be discontinued if disease progression is detected during treatment.

• Drugs that can increase WBCs, such as lithium and corticosteroids, should be used with caution while receiving Leukine. Interactions between Leukine and other drugs have not been fully evaluated.

Please see additional Important Safety Information on previous pages and full Prescribing Information available at www.leukine.com.