leukine™
sargramostim

ACTIVATE

MULTILINEAGE DEFENSE

AGAINST INFECTION WITH LEUKINE

LEUKINE™ (sargramostim) is the **first and only FDA-approved** multilineage GM-CSF that reduces the risk of infection in pediatric and adult patients following AML induction therapy or allogeneic or autologous BMT.[1]

Important Safety Information

Contraindications

- LEUKINE is contraindicated in patients with known hypersensitivity to human granulocyte-macrophage colony stimulating factor such as sargramostim (GM-CSF), yeast-derived products, or any component of LEUKINE.

Warnings and Precautions

- Serious hypersensitivity reactions, including anaphylactic reactions, have been reported with LEUKINE. If any serious allergic or anaphylactic reaction occurs, immediately discontinue LEUKINE therapy and institute medical management. Permanently discontinue LEUKINE in patients with serious allergic reactions.
- LEUKINE can cause infusion-related reactions, including respiratory distress, hypoxia, flushing, hypotension, syncope and/or tachycardia. Observe closely during infusion, particularly in patients with preexisting lung disease, as dose adjustment or discontinuation may be required.
- Do not administer LEUKINE simultaneously with or within 24 hours preceding cytotoxic chemotherapy or radiotherapy or within 24 hours following chemotherapy.

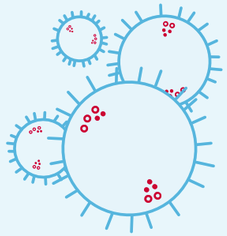
AML=acute myeloid leukemia, BMT=bone marrow transplantation, GM-CSF=granulocyte-macrophage colony-stimulating factor.

Please see continued Important Safety Information on subsequent pages, full Important Safety Information on pages 10-11, and accompanying full Prescribing Information for LEUKINE.

Fungal infection remains potentially fatal after induction therapy and hematopoietic stem cell transplant (HCT)[2,3]

Despite routine use of modern antifungals, fungal infection is still a leading cause of non-relapse mortality.[4,5]

Prevalence of infection in patients with hematologic malignancies



Studies have shown that

60%-80%

of patients who develop fungal infection die following HCT[2,3,6]

In a study of patients with AML post-induction therapy,

29%

developed multidrug-resistant organisms (MDRO)[7]

The reported incidence of fungal infection is between

6%-33%

after allogeneic HCT[4,8-11]

Fungal infection is associated with poor prognosis[4]

5.8

month median OS in patients with fungal infection

vs

76.1

month median OS in patients without fungal infection

OS=overall survival.

Fungal infection may develop months after transplantation

Several studies have shown that many cases of fungal infection occur 100+ days after HCT, when full neutropenic recovery should have already occurred.[3,4]

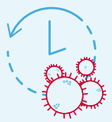
However, there are multiple factors to keep in mind that can help you identify which patients are at a higher risk for fungal infection.

Risk factors for fungal infection include[4,5,12,13]*:

Older age

Prolonged neutropenia

Persistent lymphopenia



History of prior infection

Donor type and/or allogeneic graft source

Graft-vs-host disease

Post-transplant immunosuppressants

Geography-specific epidemiology

*This is not a comprehensive list of all risk factors for fungal infection.

LEUKINE BOOSTS DEFENSE AGAINST INFECTION WITH MULTILINEAGE IMMUNE ACTIVATION

LEUKINE™ (sargramostim) is a GM-CSF that supports the survival, growth, and activation of neutrophils, monocytes/macrophages, and myeloid-derived dendritic cells.[1]

Important Safety Information (continued)

Warnings and Precautions (continued)

- Edema, capillary leak syndrome, pleural and/or pericardial effusion have been reported in patients after LEUKINE administration. LEUKINE should be used with caution and monitored in patients with preexisting fluid retention, pulmonary infiltrates, or congestive heart failure.
- Supraventricular arrhythmia has been reported in uncontrolled studies during LEUKINE administration, particularly in patients with a previous history of cardiac arrhythmia. Use LEUKINE with caution in patients with preexisting cardiac disease.
- If ANC > 20,000 cells/mm^3 or if WBC counts > 50,000/mm^3, 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.
- Treatment with LEUKINE may induce neutralizing anti-drug antibodies. Use LEUKINE for the shortest duration required.
- Liquid solutions containing benzyl alcohol (including LEUKINE Injection) or LEUKINE for Injection reconstituted with Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol) should not be administered to neonates and low birth weight infants.
- Concomitant use of drugs that can potentiate the myeloproliferative effects of LEUKINE should be avoided.

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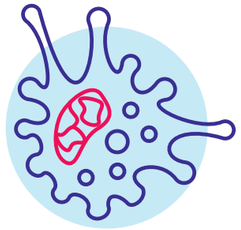
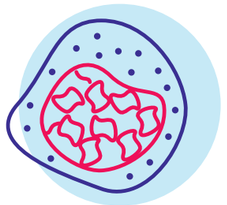


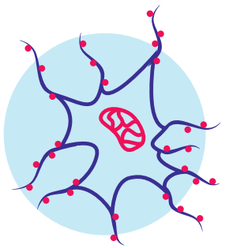
Macrophage: immune regulator

- Macrophages are highly adaptable and dynamic phagocytes that orchestrate the body's response to infection[14]
- They prime and stimulate T cells, promote tissue repair and wound healing, mediate defense against fungal and bacterial pathogens, and produce anti- and pro-inflammatory cytokines[14]
- **GM-CSF augments the ability of macrophages to phagocytize and destroy bacteria and fungi**[1,15]



Neutrophil: first responder

- Neutrophils are the first line of immune defense against invading pathogens, including bacteria, fungi, and protozoa[16]
- They phagocytize and destroy pathogens and enhance the anti-infection response of immune cells such as dendritic cells, lymphocytes, and natural killer cells[16]
- **GM-CSF enhances the chemotactic and phagocytic activity of neutrophils and extends neutrophil survival**[15]



Dendritic cell: antigen presenter

- Dendritic cells are responsible for antigen presentation and immune response regulation[17]
- They initiate long-lasting and pathogen-specific immunity[17]
- **GM-CSF links innate and adaptive immunity by inducing the growth and maturation of antigen-presenting myeloid-derived dendritic cells**[1,17]

Please see continued Important Safety Information on subsequent pages, full Important Safety Information on pages 10-11, and accompanying full Prescribing Information for LEUKINE.

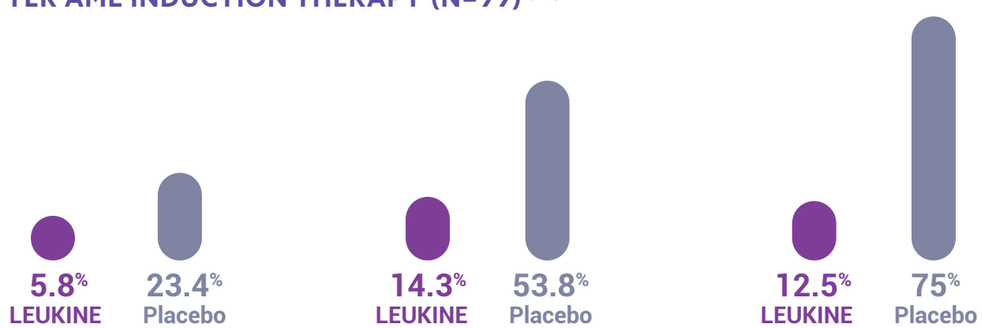
LEUKINE boosts fungicidal activity against a broad spectrum of microbes *in vitro*, including *Aspergillus fumigatus*[1,15]

Multiple benefits with multilineage defense

LEUKINE™ (sargramostim) is proven to recover neutrophil counts and reduce the risk of infection vs placebo after AML induction therapy and autologous and allogeneic BMT.[1]

LEUKINE is indicated to shorten time to neutrophil recovery and reduce the incidence of severe and life threatening infection. LEUKINE is not indicated to prevent or treat infection.[1]

SIGNIFICANTLY DECREASED INCIDENCE OF FATAL INFECTION AFTER AML INDUCTION THERAPY (N=99)[1,18,19]

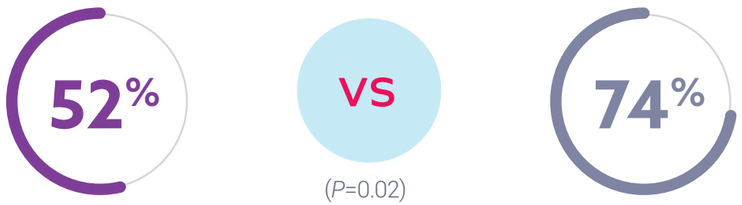


Incidence of infection-related death (*P*=0.02)

Incidence of infection-related death in patients with pneumonia

Incidence of infection-related death in patients with Grade 3 or 4 fungal infections

SIGNIFICANTLY LOWER INCIDENCE OF SERIOUS INFECTION AFTER AML INDUCTION THERAPY (N=99)[1]



of patients (n=27/52) had a Grade ≥3 infection with **LEUKINE**

(*P*=0.02)

of patients (n=35/47) had a Grade ≥3 infection with **placebo**

Important Safety Information (continued)

Adverse Reactions

Adverse events occurring in >10% of patients receiving LEUKINE in controlled clinical trials and reported in a higher frequency than placebo are:

- In Autologous bone marrow transplantation (BMT) patients—asthenia, malaise, diarrhea, rash, peripheral edema, urinary tract disorder
- 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, increase creatinine, hypomagnesemia, edema, pharyngitis, epistaxis, dyspnea, insomnia, anxiety, high glucose, low albumin

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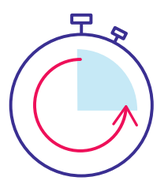
SIGNIFICANTLY SHORTENED DURATION OF INFECTION AND ANTIBACTERIAL THERAPY AFTER AUTOLOGOUS BMT (N=104)[1]

LEUKINE reduced the duration of infection by

75%

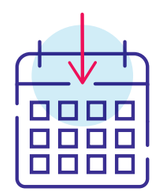
vs placebo (1 day vs 4 days, respectively)



(*P*<0.05)

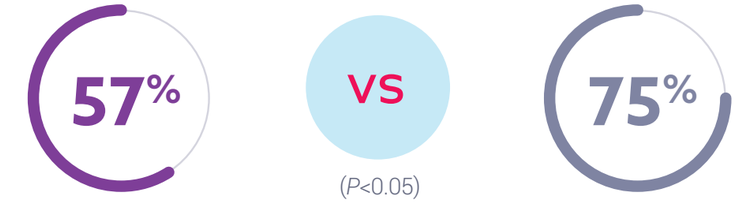
4-DAY reduction

of antibacterial therapy with **LEUKINE** vs **placebo** (21 days vs 25 days, respectively)



(*P*<0.05)

SIGNIFICANTLY REDUCED INCIDENCE OF INFECTION AND BACTEREMIA AFTER ALLOGENEIC BMT (N=109)[1]



of patients (n=30/53) treated with **LEUKINE** developed an infection

(*P*<0.05)

of patients (n=42/56) treated with **placebo** developed an infection

The incidence of bacteremia was significantly reduced with **LEUKINE** vs **placebo** following allogeneic BMT, 17% (n=9/53) vs 34% (n=19/56) of patients, respectively (*P*<0.05).[1]

Please see continued Important Safety Information on subsequent pages, full Important Safety Information on pages 10-11, and accompanying full Prescribing Information for LEUKINE.

Provide patients with multilineage defense against infection, including serious and fatal fungal infection[1,18]

LEUKINE has a well-established safety profile

The safety of LEUKINE™ (sargramostim) was demonstrated in 5 clinical trials across a range of pediatric and adult patient populations with hematologic malignancies, including AML post-induction therapy and AML, NHL, ALL, CML, Hodgkin's disease, multiple myeloma, myelodysplastic disease, and aplastic anemia post-transplant.[1]

ADVERSE REACTIONS OCCURRING IN >30% OF PATIENTS[1]

After Autologous PBPCT or BMT

Adverse reaction	LEUKINE (n=79) %	Placebo (n=77) %
Fever	95	96
Nausea	90	96
Diarrhea	89	82
Vomiting	85	90
Mucous membrane disorder	75	78
Alopecia	73	74
Asthenia	66	51
Malaise	57	51
Anorexia	54	58
Rash	44	38
GI disorder	37	47
Edema	34	35

After Allogeneic BMT

Adverse reaction	LEUKINE (n=53) %	Placebo (n=56) %
Diarrhea	81	66
Fever	77	80
Nausea	70	66
Rash	70	73
Vomiting	70	57
Stomatitis	62	63
Acute GVHD	55	59
Anorexia	51	57
High glucose	49	41
Alopecia	45	45
Abdominal pain	38	23
Low albumin	36	27
Headache	36	36
Hypertension	34	32

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AML

Adverse reaction	LEUKINE (n=52) %	Placebo (n=47) %
Fever (no infection)	81	74
Liver toxicity	77	83
Skin reactions	77	45
Infection	65	68
Metabolic laboratory abnormalities	58	49
Nausea	58	55
Diarrhea	52	53
Genitourinary abnormalities	50	57
Pulmonary toxicity	48	64
Vomiting	46	34
Neuro-clinical	42	53
Stomatitis	42	43
Alopecia	37	51
Weight loss	37	28

Understanding potential adverse reactions with LEUKINE

- Infusion-related reactions to LEUKINE can be resolved with symptomatic treatment and do not usually recur after the first administration of each cycle[1]
- Administration with LEUKINE has been associated with fever unrelated to infection. Fever may be prevented with analgesics and antipyretics such as acetaminophen[20]
- Though LEUKINE stimulates normal myeloid precursors, growth factors come with a possibility for tumor growth potentiation that cannot be excluded. LEUKINE therapy should be discontinued if disease progression is detected during treatment[1]

ALL=acute lymphoblastic leukemia, CML=chronic myeloid leukemia, GI=gastrointestinal, GVHD=graft-vs-host disease, NHL=non-Hodgkin's lymphoma, PBPCT=peripheral blood progenitor cell transplantation.

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Important Safety Information

Contraindications

- LEUKINE™ (sargramostim) is contraindicated in patients with known hypersensitivity to human granulocyte-macrophage colony stimulating factor such as sargramostim (GM-CSF), yeast-derived products, or any component of LEUKINE

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Adverse Reactions

Adverse events occurring in >10% of patients receiving LEUKINE in controlled clinical trials and reported in a higher frequency than placebo are:

- In Autologous bone marrow transplantation (BMT) patients—asthenia, malaise, diarrhea, rash, peripheral edema, urinary tract disorder
- 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, increase creatinine, hypomagnesemia, edema, pharyngitis, epistaxis, dyspnea, insomnia, anxiety, high glucose, low albumin
- In AML patients—fever, weight loss, nausea, vomiting, anorexia, skin reactions, metabolic laboratory abnormalities, edema

Indications and Usage

LEUKINE is a leukocyte growth factor indicated for the following uses:

- 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).
- 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.
- 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).
- 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.
- 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.

Please see accompanying full Prescribing Information for LEUKINE.

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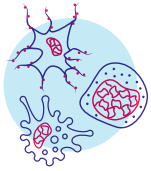
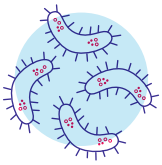
THE FIRST AND ONLY FDA-APPROVED

MULTILINEAGE GM-CSF THAT RECOVERS ANC AND LOWERS INCIDENCE OF INFECTION AND INFECTION-RELATED OUTCOMES[1]



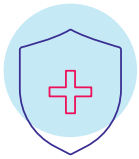
Multilineage immune activation

LEUKINE™ (sargramostim) is a GM-CSF that supports the survival, growth, and activation of neutrophils, monocytes/macrophages, and myeloid-derived dendritic cells.[1]



Proven anti-infection defense

- LEUKINE significantly reduced the incidence of infection and infection-related deaths vs placebo in adult patients with AML following induction chemotherapy[1,18,19]
- LEUKINE demonstrated significantly improved anti-infection benefits vs placebo in pediatric and adult patients undergoing allogeneic or autologous BMT[1]



Well-established safety profile

The safety of LEUKINE was demonstrated in 5 clinical trials across a range of pediatric and adult patient populations with hematologic malignancies, including AML post-induction therapy and AML, NHL, ALL, CML, Hodgkin's disease, multiple myeloma, myelodysplastic disease, and aplastic anemia post-transplant.[1]

Consider LEUKINE for your patients at increased risk of infection following AML induction therapy or allogeneic or autologous BMT[1]

Important Safety Information (continued)

Adverse Reactions (continued)

Adverse events occurring in >10% of patients receiving LEUKINE in controlled clinical trials and reported in a higher frequency than placebo are:

- In AML patients—fever, weight loss, nausea, vomiting, anorexia, skin reactions, metabolic laboratory abnormalities, edema

ANC=absolute neutrophil count.

References: **1.** Leukine [package insert]. Lexington, MA: Partner Therapeutics, Inc.; 2018. **2.** Parody R, Martino R, Rovira M, et al; Infectious/Non-infectious Complications Subcommittee of the Grupo Español de Trasplante Hematopoyético (GETH). *Biol Blood Marrow Transplant*. 2006;12(7):734-748. **3.** Schuster MG, Cleveland AA, Dubberke ER, et al. *Open Forum Infect Dis*. 2017;4(2):ofx050. **4.** Omer AK, Ziakas PD, Anagnostou T, et al. *Biol Blood Marrow Transplant*. 2013;19(8):1190-1196. **5.** Mehta RS, Rezvani K. *Virulence*. 2016;7(8):901-916. **6.** Kriengkauykiat J, Ito JI, Dadwal SS. *Clin Epidemiol*. 2011;3:175-191. **7.** Ballo O, Tarazzit I, Stratmann J, et al. *PLoS One*. 2019;14(1):e0210991. **8.** Jantunen E, Nihtinen A, Volin L, et al. *Bone Marrow Transplant*. 200;34(10):891-895. **9.** Martino R, Subirá M, Rovira M, et al; alloPBSCT Infectious/Non-infectious Complications Subcommittees of the Grupo Español de Trasplante Hematopoyético (GETH). *Br J Haematol*. 2002;116(2):475-482. **10.** Hagen EA, Stern H, Porter D, et al. *Clin Infect Dis*. 2003;36(1):9-15. **11.** Camps IR. *Int J Antimicrob Agents*. 2008;32(suppl 2):S119-S123. **12.** Nucci M, Anaissie E. *Blood*. 2014;124(26):3858-3869. **13.** National Cancer Institute website. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/lymphopenia. Accessed June 11, 2019. **14.** Shapouri-Moghaddam A, Mohammadian S, Vazini H, et al. *J Cell Physiol*. 2018;233(9):6425-6440. **15.** Armitage JO. *Blood*. 1998;92(12):4491-4508. **16.** Mayadas TN, Cullere X, Lowell CA. *Annu Rev Pathol*. 2014;9:181-218. **17.** Mellman I. *Cancer Immunol Res*. 2013;1(3):145-149. **18.** Rowe JM, Rubin A, Mazza JJ, et al. In: Hiddemann W, Büchner T, Wörmann B, et al, eds. *Acute Leukemias V: Experimental Approaches and Management of Refractory Diseases*. Berlin: Springer; 1996:178-184. **19.** Rowe JM, Andersen JW, Mazza JJ, et al. *Blood*. 1995;86(2):457-462. **20.** Buchsel PC, Forgey A, Grape FB, Hamann SS. *Clin J Oncol Nurs*. 2002;6(4):198-205.

Please see full Important Safety Information on pages 10-11 and accompanying full Prescribing Information for LEUKINE.

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