POLICY: Gamifant Utilization Management Medical Policy

- Gamifant® (emapalumab-lzsg intravenous infusion – Sobi)

EFFECTIVE DATE: 1/1/2020
LAST REVISION DATE: 07/16/2025

COVERAGE CRITERIA FOR: All UCare Plans

OVERVIEW

Gamifant, an anti-interferon gamma (IFN-γ) antibody, is indicated for the treatment of:[1]

- **Primary hemophagocytic lymphohistiocytosis** (HLH) in adult and pediatric patients with refractory, recurrent, or progressive disease, or intolerance with conventional HLH therapy.
- **HLH/Macrophage activation syndrome (MAS)** in adult and pediatric patients with known or suspected Still's disease including systemic juvenile idiopathic arthritis (sJIA), with an inadequate response or intolerance to glucocorticoids, or with recurrent MAS.

Disease Overview

HLH is a syndrome characterized by signs and symptoms of extreme inflammation, that often lead to multiorgan failure and death if not treated promptly.[2] It is classified as either primary, resulting from inherited genetic mutations, or secondary (MAS), often triggered by infection, malignancy, or rheumatologic condition. Clinically, HLH manifests with nonspecific signs indicative of systemic inflammation.[3] These may include prolonged fever, cytopenias, hepatosplenomegaly, and elevated inflammatory markers like ferritin. In addition, neurological symptoms, liver dysfunction, and respiratory distress may also occur. In healthy individuals, cytotoxic function is important to terminate immune responses when appropriate by targeting and destroying activated immune cells.[2] Deficiencies in cytotoxic function lead to an unchecked immune response and hyper-inflammation. Primary HLH has a clear genetic cause, whereas secondary HLH is triggered by a concomitant infection or medical condition, such as Epstein-Barr virus infection, malignancy, or rheumatologic disorders. IFN-γ plays a pivotal role in both primary and secondary HLH and has both pro-inflammatory functions (e.g., macrophage activation) and anti-inflammatory functions (e.g., activation of cytotoxic cells). However, in HLH, the anti-inflammatory action of IFN-γ is ineffective due to impaired cytotoxic cell activity; thus, pro-inflammatory effects predominate.

Guidelines

The HLH-2004 treatment protocol, developed by the Histiocyte Society, is the current standard of care for diagnostic and therapeutic management of primary HLH.[4] Gamifant is not addressed in the 2004 protocol. To establish a diagnosis of HLH, patients must either have a molecular diagnosis consistent with HLH or must meet five out of eight diagnostic criteria. A backbone of etoposide and systemic dexamethasone is the conventional standard of care to induce symptomatic resolution; cyclosporine A and anti-thymocyte globulin have also demonstrated efficacy. Although chemotherapy prolongs survival in primary HLH, a hematopoietic stem cell transplant (HSCT) is needed for cure. Patients with primary HLH should continue chemotherapy (usually with etoposide, cyclosporine A, and dexamethasone) until HSCT can be performed. Myelotoxicity due to chemotherapy is a concern, especially since patients with HLH can have severe cytopenias and immunodeficiency at baseline. Regarding secondary HLH (MAS), the European Alliance of Associations for Rheumatology (EULAR) and Pediatric Rheumatology European Society (PReS) joint

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clinical guidelines recognize high dose corticosteroids as the mainstay of treatment.[5] In addition, treatments including anakinra, cyclosporine and/or Gamifant should be considered as part of initial therapy.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Gamifant. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Gamifant, approval requires it to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Gamifant is recommended in those who meet the following criteria:

FDA-Approved Indication

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1. **Hemophagocytic Lymphohistiocytosis, Primary.** Approve Gamifant for 6 months if the patient meets the following (A, B, C, and D):
   - **A)** Patient has a diagnosis of primary hemophagocytic lymphohistiocytosis determined by at least ONE of the following (i or ii):
     - **i.** Patient has a molecular genetic diagnosis consistent with primary hemophagocytic lymphohistiocytosis; OR
     - **ii.** Prior to treatment, the patient meets at least FIVE of the following diagnostic criteria at baseline (FIVE of a, b, c, d, e, f, g, or h):
       - **a)** Fever ≥ 38.5° C; OR
       - **b)** Splenomegaly; OR
       - **c)** Cytopenias defined as at least TWO of the following (TWO of 1, 2, or 3):
         - **1)** Hemoglobin < 9 g/dL (or < 10 g/dL in infants less than 4 weeks of age); OR
         - **2)** Platelets < 100 x 10^9/L; OR
         - **3)** Neutrophils < 1.0 x 10^9/L; OR
       - **d)** Patient meets ONE of the following (1 or 2):
         - **1)** Fasting triglycerides ≥ 265 mg/dL; OR
         - **2)** Fibrinogen ≤ 1.5 g/L; OR
       - **e)** Hemophagocytosis in bone marrow, spleen, or lymph nodes; OR
       - **f)** Low or absent natural killer cell activity (according to local laboratory reference); OR
       - **g)** Ferritin ≥ 500 mcg/L; OR
       - **h)** Soluble CD25 (i.e., soluble interleukin-2 receptor) ≥ 2,400 U/mL; AND
   - **B)** Patient has tried at least one conventional therapy (e.g., etoposide, cyclosporine A, or anti-thymocyte globulin); AND
   - **C)** According to the prescriber, the patient has experienced at least one of the following (i or ii):
     - **i.** Refractory, recurrent, or progressive disease during conventional therapy (e.g., etoposide, cyclosporine A, or anti-thymocyte globulin); OR
     - **ii.** Intolerance to conventional therapy (e.g., etoposide, cyclosporine A, or anti-thymocyte globulin); AND

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D) The medication is prescribed by or in consultation with a hematologist, oncologist, immunologist, transplant specialist, or physician who specializes in hemophagocytic lymphohistiocytosis or related disorders.

Dosing. Approve up to a maximum dose of 10 mg/kg by intravenous infusion, not more frequently than twice weekly (once every 3 to 4 days).

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2. Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS). Approve Gamifant for 8 weeks if the patient ALL of the following (A, B, C, and D):

Note: HLH/MAS is a form of secondary HLH.

A) Patient has a confirmed or suspected diagnosis of systemic juvenile idiopathic arthritis or Still's disease, adult onset; AND

B) Prior to treatment, patient has a ferritin level > 684 ng/mL and at least TWO of the following diagnostic criteria at baseline (TWO of i, ii, iii, or iv)

- **i.** Platelets ≤ 181 x 10^9/L; OR
- **ii.** AST > 48 U/L; OR
- **iii.** Fasting triglyceride > 156 mg/dL; OR
- **iv.** Fibrinogen ≤ 360 mg/dL; AND

C) Patient meets ONE of the following (i or ii):

- **i.** According to the prescriber, the patient has had an inadequate response or intolerance to high-dose intravenous corticosteroids; OR
- **ii.** Patient has previously received therapy with Gamifant; AND

D) The medication is prescribed by or in consultation with a hematologist, oncologist, immunologist, rheumatologist, or physician who specializes in hemophagocytic lymphohistiocytosis or related disorders.

Dosing. Approve up to a maximum dose of 10 mg/kg by intravenous infusion, not more frequently than once daily.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Gamifant is not recommended in the following situations:

1. Use for Secondary Hemophagocytic Lymphohistiocytosis (HLH). Current data is lacking support for the treatment of secondary HLH using Gamifant (emapalumab-lzsg) and use is not FDA approved.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Gamifant® intravenous infusion [prescribing information]. Waltham, MA: Sobi; June 2025.
2. Henter JI. Hemophagocytic Lymphohistiocytosis. *N Engl J Med.* 2025 Feb 6;392(6):584-598.
3. Konkol S, Killeen RB, Rai M. Hemophagocytic Lymphohistiocytosis. [Updated 2025 May 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557776/. Accessed on: July 7, 2025.
4. Henter J, Horne A, Aricó M, et al. HLH-2004: Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48:124-131.

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5. Fautrel B, Mitrovic S, De Matteis A, et al. EULAR/PReS recommendations for the diagnosis and management of Still's disease, comprising systemic juve nile idiopathic arthritis and adult-onset Still's disease. *Ann Rheum Dis.* 2024;83(12):1614-1627.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	12/02/2020
Annual Revision	No criteria changes.	12/22/2021
UCare Revision	Updated Conditions Not Recommended for Approval section to include Secondary Hemophagocytic Lymphohistiocytosis	12/16/2022
Annual Revision	No criteria changes.	02/14/2024
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/16/2024
Annual Revision	No criteria changes.	01/08/2025
Early Annual Revision	**Hemophagocytic Lymphohistiocytosis, Primary:** In criteria for diagnosis, added the term "primary" before hemophagocytic lymphohistiocytosis. **Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS):** This new condition of approval was added.	07/16/2025
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process.	09/15/2025

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