Drug Coverage Policy

Effective Date.....9/15/2025
Coverage Policy Number.....IP0113
Policy Title.....Gamifant

Gamifant

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

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Medical Necessity Criteria

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information.

Gamifant is considered medically necessary when ONE of the following criteria are met (1 or 2):

1. **Hemophagocytic Lymphohistiocytosis, Primary.** Individual meets **ALL** the following criteria:
    A. Diagnosis of primary hemophagocytic lymphohistiocytosis confirmed by **ONE** of the following **[documentation required]:**
        i. Molecular genetic diagnosis consistent with primary hemophagocytic lymphohistiocytosis (for example, confirmed bi-allelic pathogenic or likely

pathogenic variants in AP3B1, LYST, PRF1, UNC13D/Munc13-4, STX11, STXBP2, RAB27a, XIAP/BIRC4 or SH2D1A)

ii. Documentation of at least **FIVE** of the following diagnostic criteria from the American Histiocyte Society (at baseline prior to treatment):
   a. Persistent fever
   b. Splenomegaly
   c. Cytopenia involving at least 2 cell lines (hemoglobin less than 9 g/dL or less than 10 g/dL in infants less than 4 weeks of age, absolute neutrophil count less than 1000/µL, platelets less than 100,000/µL)
   d. Hypertriglyceridemia (fasting triglycerides 265mg/dL or greater) or hypofibrinogenemia (fibrinogen less than 1.5 g/L or greater than 3 standard deviations less than normal value for age)
   e. Hemophagocytosis in bone marrow, spleen, or lymph nodes with no evidence of malignancy
   f. Low or absent natural killer (NK)-cell activity
   g. Serum ferritin greater than 500 mcg/L
   h. Elevated soluble interleukin-2 (CD25) levels (greater than 2400 U/mL or very high for age)

B. Evidence of active disease (for example, fever, splenomegaly, central nervous system symptoms, cytopenia, elevated fibrinogen and/or D-dimer, elevated ferritin, and elevated soluble CD25 [also referred to as soluble interleukin-2 receptor] levels)

C. Refractory, recurrent, or progressive disease during conventional HLH therapy OR has demonstrated an intolerance to conventional HLH therapy (examples of conventional therapy include, etoposide, corticosteroids, cyclosporine, anti-thymocyte globulin, methotrexate)

D. 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. 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).** Individual meets 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) **[documentation required]:**
      i. Platelets $\leq$ 181 x 10^9/L; OR
      ii. AST > 48 U/L; OR
      iii. Fasting triglyceride > 156 mg/dL; OR
      iv. Fibrinogen $\leq$ 360 mg/dL

   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.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Reauthorization Criteria

Continuation of emapalumab-lzsg (Gamifant) is considered medically necessary when the above medical necessity criteria are met and **ALL** the following:

1. Documentation of clinical response (improvement in any of the clinical or laboratory parameters used to demonstrate evidence of active disease on initial authorization), but also evidence of residual active disease.
2. Dose titration has occurred to the minimum dose and frequency to achieve sustained clinical effect as recommended by FDA labeling of emapalumab-lzsg (Gamifant).

Authorization Duration

Hemophagocytic Lymphohistiocytosis, Primary
Initial approval duration: up to 6 months
Reauthorization approval duration: up to 6 months

Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS).
Initial approval duration: up to 8 months
Reauthorization approval duration: up to 8 months

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven.

Coding Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J9210	Injection, emapalumab-lzsg, 1 mg

Background

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 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.

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.

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.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	No criteria changes.	05/01/2024
Annual Revision	No criteria change.	4/15/2025
Selected Revision	**Added "<u>Documentation</u>:** Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information." **Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS):** This new condition of approval was added.	9/15/2025

The policy effective date is in force until updated or retired.