

emapalumab-lzsg (Gamifant™)

Policy # 00678

Original Effective Date: 07/18/2019

Current Effective Date: 08/01/2026

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member's contract/certificate, and
- Medical necessity criteria and guidelines are met.

Primary Hemophagocytic Lymphohistiocytosis (HLH)

Based on review of available data, the Company may consider emapalumab-lzsg (Gamifant™)† for the treatment of primary hemophagocytic lymphohistiocytosis (HLH) to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for the use of emapalumab-lzsg (Gamifant) for the treatment of primary hemophagocytic lymphohistiocytosis (HLH) will be considered when the following criteria are met:

Initial

- Patient has a diagnosis of primary hemophagocytic lymphohistiocytosis (HLH) determined by at least ONE of the following:
 - Documentation of genetic testing demonstrating homozygosity or compound heterozygosity for verified HLH-associated mutations (e.g., *PRF1*, *UNC13D*, *STX11*, *STXBP2*, *Rab27A*, *SH2D1A*, *BIRC4*, *LYST*, *ITK*, *SLC7A7*, *XMEN*, *HPS*); OR
 - Prior to treatment, the patient meets at least FIVE of the following diagnostic criteria:
 - Fever greater than or equal to 38.5°C (101.3°F); OR
 - Splenomegaly; OR
 - Cytopenias defined as at least TWO of the following:
 - ❖ Hemoglobin less than 9 g/dL (or less than 10 g/dL in infants less than 4 weeks of age); OR
 - ❖ Platelets less than 100 x10⁹/L; OR
 - ❖ Neutrophils less than 1x10⁹/L; OR
 - ❖ Fasting triglycerides greater than or equal to 265 mg/dL OR fibrinogen less than or equal to 1.5 g/L; OR
 - ❖ Hemophagocytosis in bone marrow, spleen, or lymph nodes; OR
 - ❖ Low or absent natural killer cell activity (according to local laboratory reference); OR

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- ❖ Ferritin greater than or equal to 500 mcg/L; OR
- ❖ Soluble CD25 (i.e., soluble interleukin-2 receptor) greater than or equal to 2,400 Units/mL; AND
- Patient has tried at least one conventional therapy (e.g., etoposide, cyclosporine A, or anti-thymocyte globulin); AND
- According to the prescriber, patient has experienced at least ONE of the following:
 - Refractory, recurrent, or progressive disease during conventional therapy (e.g., etoposide, cyclosporine A, or anti-thymocyte globulin); OR
 - Intolerance to conventional therapy (e.g., etoposide, cyclosporine A, or anti-thymocyte globulin); AND
- Patient has NOT received a hematopoietic cell transplant (HCT); AND
*(Note: This specific patient selection criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient does NOT have secondary HLH (e.g., HLH associated with rheumatic or neoplastic disease); AND
- Gamifant will be administered with dexamethasone; AND
- Patient does NOT have an active infection with a pathogen that is favored by interferon gamma (IFN γ) neutralization (e.g. mycobacteria, Herpes Zoster, *Histoplasma capsulatum*); AND
- Patient will receive prophylaxis for Herpes Zoster, *Pneumocystis jirovecii*, fungal infections, and tuberculosis (if PPD positive); AND
- Dose will not exceed 10 mg/kg administered twice per week.

Continuation

- Patient has received an initial authorization for Gamifant; AND
- Patient has had a beneficial response to treatment based on documented improvement in THREE or more signs of HLH abnormalities; AND
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient is awaiting HCT or is not a candidate for HCT; AND
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Dose will not exceed 10 mg/kg administered twice per week.

Hemophagocytic Lymphohistiocytosis/ Macrophage Activation Syndrome (HLH/MAS)

Based on review of available data, the Company may consider emapalumab-lzsg (Gamifant) for the treatment of hemophagocytic lymphohistiocytosis/ Macrophage Activation Syndrome (HLH/MAS) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of emapalumab-lzsg (Gamifant) for the treatment of hemophagocytic lymphohistiocytosis/ macrophage activation syndrome (HLH/MAS) will be considered when the following criteria are met:

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Initial

- Patient has a diagnosis of hemophagocytic lymphohistiocytosis/ macrophage activation syndrome (HLH/MAS); AND
- Patient has known or suspected diagnosis of systemic juvenile idiopathic arthritis (sJIA) or Still's disease, adult onset (AOSD); AND
- Prior to treatment, patient has a diagnosis of macrophage activation syndrome (MAS) as evidenced by a ferritin level greater than 684 ng/mL and at least TWO of the following diagnostic criteria:
 - Platelets less than or equal to 181×10^9 ; OR
 - AST greater than 48 U/L; OR
 - Fasting triglyceride greater than 156 mg/dL; OR
 - Fibrinogen less than or equal to 360 mg/dL; AND
- Patient has had an inadequate response or intolerance to high-dose intravenous corticosteroids; AND
- Dose will not exceed the FDA-labeled dose of 6 mg/kg on day 1 followed by 3 mg/kg every 3 days for 5 doses followed by 3 mg/kg twice weekly.

Continuation

- Patient has received an initial authorization for Gamifant for HLH/MAS; AND
- Patient has experienced a positive clinical response to Gamifant as attested by the prescriber; AND
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Dose will not exceed the FDA-labeled dose of 6 mg/kg on day 1 followed by 3 mg/kg every 3 days for 5 doses followed by 3 mg/kg twice weekly.

When Services Are Considered Not Medically Necessary

The use of emapalumab-lzsg (Gamifant) for primary HLH when the patient has received a hematopoietic cell transplant (HCT) or has not experienced a beneficial response to Gamifant treatment is considered to be **not medically necessary.****

The continued use of emapalumab-lzsg (Gamifant) for primary HLH or HLH/MAS when the patient has not experienced a positive clinical response to treatment is considered to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of emapalumab-lzsg (Gamifant) when the patient selection criteria are not met (except those noted to be **not medically necessary****) to be **investigational.***

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Background/Overview

Gamifant is a monoclonal antibody that binds to and neutralizes interferon gamma (IFN γ), a cytokine that is hypersecreted in hemophagocytic lymphohistiocytosis (HLH). It is indicated for patients with primary HLH that is refractory, recurrent, or progressive after conventional therapy has been tried. It is also indicated for patients with HLH/ macrophage activation syndrome (MAS). For primary HLH, Gamifant is administered as an intravenous infusion twice per week with an initial dose of 1 mg/kg that can be increased up to 10 mg/kg. Dose increases are based on the healthcare provider's assessment of improvement in clinical condition and additional parameters listed in the drug's package insert. Additionally, systemic dexamethasone and prophylaxis for Herpes Zoster, *Pneumocystis jirovecii*, and fungal infections should be administered concomitantly with Gamifant. For HLH/MAS, Gamifant is administered as 6 mg/kg IV on day 1 followed by 3 mg/kg every 3 days for 5 doses followed by 3 mg/kg twice weekly until the patient no longer requires therapy for the treatment of HLH/MAS.

Primary HLH is a primarily pediatric, ultra-rare, rapidly progressive, hyperinflammatory syndrome caused by massive hyperproduction of interferon gamma (IFN γ) that may lead to organ failure and death if not appropriately treated. It is caused by defects in cytotoxic function that lead to over-activation of the immune system. The incidence is estimated at 1.2 cases per million individuals per year. Primary HLH differs from secondary HLH in that it has a clear genetic cause, whereas secondary HLH is triggered by concomitant infection or medical condition such as Epstein-Barr Virus (EBV) infection, malignancy, or rheumatologic disorders. Prior to Gamifant, no therapies were approved by the Food and Drug Administration (FDA) for the treatment of primary HLH. Steroids and chemotherapy are typically used off-label prior to hematopoietic cell transplantation (HCT).

The HLH-2004 treatment protocol, developed by the Histiocyte Society, is the current standard of care for diagnostic and therapeutic guidelines. According to these guidelines, diagnosis must be established by a molecular genetic diagnosis consistent with HLH or five of eight clinical criteria suggesting HLH. Conventional standard of care to induce symptomatic resolution is etoposide and systemic dexamethasone. Cyclosporine A and anti-thymocyte globulin have also demonstrated efficacy. All patients should receive an initial 8 weeks of induction chemotherapy which is known to prolong survival. In primary HLH, HCT is necessary to cure the patient, so patients should continue standard therapy until HCT can be performed. These guidelines do not mention Gamifant, but the FDA has indicated in the approved label that its place in therapy is in patients who failed or cannot tolerate standard therapy for primary HLH.

Hemophagocytic lymphohistiocytosis/ macrophage activation syndrome (HLH/MAS) is a rare, potentially life-threatening hyperinflammatory condition driven by excessive immune activation and uncontrolled cytokine release, particularly interferon gamma (IFN γ). HLH may be primary (genetic) or secondary to underlying conditions such as infections, malignancies, or rheumatologic diseases, while MAS represents a form of secondary HLH most commonly associated with Still's disease, including systemic juvenile idiopathic arthritis and adult-onset Still's disease. The condition is characterized by impaired cytotoxic function of natural killer (NK) cells and cytotoxic T lymphocytes, leading to persistent activation of macrophages and lymphocytes. Clinically,

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HLH/MAS presents with features such as prolonged fever, cytopenias, hyperferritinemia, coagulopathy, elevated liver enzymes, and organomegaly, and may rapidly progress to multiorgan failure if not promptly treated.

Treatment typically involves rapid initiation of immunosuppressive and cytotoxic therapies to control hyperinflammation. Conventional management includes high-dose corticosteroids and etoposide-based regimens, often in combination with cyclosporine A. Additional therapies used in selected patients include anti-thymocyte globulin, intravenous immunoglobulin (IVIG), and biologic agents targeting inflammatory cytokines such as anakinra (IL-1 inhibition) or tocilizumab (IL-6 inhibition). Hematopoietic cell transplantation (HCT) is considered curative for primary HLH and may be required in refractory cases. More recently, targeted therapies such as Gamifant have been developed to address the underlying cytokine dysregulation in patients with refractory or specific forms of HLH/MAS.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Gamifant was approved in 2018 for the treatment of adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy. In June 2025, Gamifant received an additional approval for the treatment of adult and pediatric patients with HLH/macrophage activation syndrome (MAS) in known or suspected Still's disease, including systemic Juvenile Idiopathic Arthritis (sJIA), with an inadequate response or intolerance to glucocorticoids, or with recurrent MAS.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Primary HLH

The efficacy of Gamifant was evaluated in a multicenter, open-label, single-arm trial in 27 pediatric patients with suspected or confirmed primary HLH with either refractory, recurrent, or progressive disease during conventional HLH therapy or who were intolerant of conventional HLH therapy. Enrolled patients had primary HLH based on a molecular diagnosis or family history consistent with primary HLH or 5 out of the 8 criteria fulfilled: fever, splenomegaly, cytopenias affecting 2 of 3 lineages in the peripheral blood, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in bone marrow, spleen or lymph nodes with no evidence of malignancy, low or absent NK-cell activity, ferritin ≥ 500 mcg/L, soluble CD25 ≥ 2400 U/mL. Additionally, patients had to have evidence of active disease as assessed by the treating physician. Included patients also had not responded, not achieved or maintained a satisfactory response, or were intolerant to conventional HLH treatments.

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The study treatment duration was up to 8 weeks after which patients could continue treatment in the extension study. All patients received an initial starting dose of Gamifant of 1 mg/kg every 3 days. Subsequent doses could be increased to a maximum of 10 mg/kg based on clinical and laboratory parameters interpreted as unsatisfactory response. Throughout the study, 44% of patients remained at a dose of 1 mg/kg, 30% of patients increased to 3-4 mg/kg, and 26% of patients increased to 6-10 mg/kg. The median time to dose increase was 27 days with 22% of patients requiring a dose increase in the first week of treatment. All patients received dexamethasone as background HLH treatment. Cyclosporine A was continued if administered prior to screening. Patients receiving methotrexate and glucocorticoids administered intrathecally at baseline could continue these treatments.

The efficacy of Gamifant was based upon overall response rate (ORR) at the end of treatment, defined as achievement of either a complete or partial response or HLH improvement. ORR was evaluated using an algorithm that included the following objective clinical and laboratory parameters: fever, splenomegaly, CNS symptoms, complete blood count, fibrinogen and/or D-dimer, ferritin, and soluble CD25 levels. Complete response was defined as normalization of all HLH abnormalities. Partial response was defined as normalization of ≥ 3 HLH abnormalities. HLH improvement was defined as ≥ 3 HLH abnormalities improved by at least 50% from baseline. At the end of treatment, the ORR was found to be 63% (95% CI 0.42, 0.81) with 26% being complete responses, 30% partial responses, and 7.4% HLH improvements.

HLH/MAS

The efficacy of Gamifant was evaluated in two open-label, single-arm, multicenter studies (NI-0501-06 and NI-0501-14) which enrolled a total of 39 adult and pediatric patients with hemophagocytic lymphohistiocytosis (HLH)/ macrophage activation syndrome (MAS) in Still's disease, including systemic juvenile idiopathic arthritis (sJIA), who had an inadequate response to high-dose intravenous glucocorticoids. Enrollment criteria required a confirmed or suspected diagnosis of sJIA or adult-onset Still's disease and active MAS defined by ferritin > 684 ng/mL and at least two additional laboratory abnormalities (platelet count $\leq 181 \times 10^9/L$, AST > 48 U/L, triglycerides > 156 mg/dL, or fibrinogen ≤ 360 mg/dL). Patients with infections associated with interferon gamma neutralization risk (e.g., mycobacterial or fungal infections) were excluded.

Patients received Gamifant at an initial dose of 6 mg/kg followed by at least 3 mg/kg every 3 days through Day 16, and then twice weekly thereafter. Concomitant glucocorticoids and low-dose anakinra were permitted. In the pooled analysis, 39 patients were treated, of whom 95% completed the studies. The median age was 12 years (range 0.9 to 64), and the majority were female (80%). At baseline, patients demonstrated marked hyperinflammation, including elevated ferritin, liver enzymes, and LDH.

Efficacy was assessed by complete response (CR), defined as resolution of clinical signs and symptoms (visual analog scale ≤ 1 cm) together with normalization or improvement of laboratory parameters, including hematologic values, liver enzymes, fibrinogen, LDH, and ferritin. At Week 8, 53.8% of patients (21/39; 95% CI: 37.2–69.9) achieved a complete response.

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References

1. Gamifant [package insert]. Swedish Orphan Biovitrum AB. Stockholm, Sweden. Updated March 2026.
2. Gamifant Prior Authorization Policy. Express Scripts. July 2025.
3. Gamifant New Drug Approval. IPD Analytics. November 2018.

Policy History

Original Effective Date: 07/18/2019

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07/03/2019 Medical Policy Committee review

07/18/2019 Medical Policy Implementation Committee approval. New policy.

07/02/2020 Medical Policy Committee review

07/08/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

07/01/2021 Medical Policy Committee review

07/14/2021 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

07/07/2022 Medical Policy Committee review

07/13/2022 Medical Policy Implementation Committee approval. No change to coverage.

07/06/2023 Medical Policy Committee review

07/12/2023 Medical Policy Implementation Committee approval. No change to coverage.

07/02/2024 Medical Policy Committee review

07/10/2024 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

07/03/2025 Medical Policy Committee review

07/09/2025 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

07/21/2026 Pre-Pharmacy and Therapeutics Committee approval

07/22/2026 Pharmacy and Therapeutics Committee approval. Updated criteria and background information to reflect new indication for HLH/MAS.

Next Scheduled Review Date: 07/2027

Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2025 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Louisiana Blue Medical Policy Coverage Guidelines is with Louisiana Blue and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Louisiana Blue Medical Policy Coverage Guidelines.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J9210
ICD-10 Diagnosis	All Related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

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- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan’s authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan’s pharmacy benefit.