Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

Medical benefit drug policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and therefore subject to change.

P&T Date: 08/07/2025

Gamifant® (emapalumab-lzsg)

HCPCS: J9210

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. FDA approved indication
   b. FDA approved age
   c. Diagnosis of primary (familial) hemophagocytic lymphohistiocytosis (HLH)
      i. Must meet one of the following:
         1. Biallelic pathogenic gene mutation in either the PRF1, UNC13D, STX11, or STXBP2 genes with signs and symptoms of HLH
         2. Absent or low perforin expression or defective or impaired cytotoxic lymphocyte exocytosis with signs and symptoms of HLH
         3. Must meet 5 out of the following criteria:
            a) Fever greater than or equal to $38.5^{o}C$
            b) Splenomegaly
            c) Cytopenias affecting greater than or equal to 2 of 3 lineages in the peripheral blood
               1) Hemoglobin less than 90 g/L (in infants less than 4 weeks of age, hemoglobin less than 100 g/L)
               2) Platelets less than $100 \times 10^{9}/L$
               3) Neutrophils less than $1.0 \times 10^{9}/L$
            d) Hypertriglyceridemia and/or hypofibrinogenemia:
               1) Fasting triglycerides greater than or equal to 3.0 mmol/L
               2) Fibrinogen less than or equal to 1.5 g/L
            e) Hemophagocytosis in the bone marrow, spleen, or lymph nodes
            f) Ferritin greater than or equal to 500 µg/L
            g) Soluble CD25 greater than or equal 2,400 U/mL
      ii. Must be used in combination with dexamethasone
      iii. Refractory, recurrent, or progressive disease or intolerance with conventional HLH therapy with dexamethasone and etoposide defined as:
         1. Having not responded or not achieved a satisfactory response to conventional therapy OR
         2. Having not maintained a satisfactory response to conventional therapy OR

3. Intolerance to conventional therapy

d. Diagnosis HLH/macrophage activation syndrome (MAS)
    i. Must have ferritin greater than 684 ng/mL and any 2 of the following:
        1. Platelet count less than or equal to 181 x 10^9/L
        2. Aspartate aminotransferase (AST) greater than 48 U/L
        3. Triglycerides greater than 156 mg/dL
        4. Fibrinogen less than or equal to 360 mg/dL
    ii. Must be diagnosed with systemic juvenile idiopathic arthritis or adult onset Still's disease
    iii. Must have had an inadequate response to high-dose intravenous glucocorticoids defined as greater than or equal to 2 mg/kg/day of prednisone equivalent in two divided doses or at least 60 mg/day in patients weighing 30 kg or more, including but not limited to, pulses up to 30 mg/kg/day for at least 3 consecutive days
e. Trial and failure, contraindication, or intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list

B. Quantity Limitations, Authorization Period and Renewal Criteria
    a. Quantity Limits: Align with FDA recommended dosing
    b. Authorization Period: One year at a time
    c. Renewal Criteria: Clinical documentation must be provided to confirm that current criteria are met and that the medication is providing clinical benefit

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- Hemophagocytic lymphohistiocytosis (HLH)

    - Hemophagocytic lymphohistiocytosis (HLH) is a rare, severe condition caused by an overactive, abnormal response of the immune system. It is characterized by overwhelming inflammation that often leads to multiorgan failure and death if not treated promptly and appropriately. In HLH, the immune system responds to a stimulus or trigger, often an infection, but the response is ineffective and abnormal. The ineffective, abnormal response causes a variety of signs and symptoms, which, if not treated, can potentially become life-threatening.

    - The onset and severity of HLH can vary greatly from one person to another. The specific symptoms that develop can also vary greatly, although the condition often causes multiorgan involvement. Generally, affected individuals develop fevers, a rash, hepatomegaly, and splenomegaly. Fevers may be prolonged and persistent, often failing to respond to antibiotics. Sometimes, the lymph nodes are also abnormally large. Other symptoms include anemia, thrombocytopenia, seizures, changes in mental status, irritability, and ataxia. Additional symptoms can occur depending upon the specific organ system involved in an individual.

    - HLH is broadly broken down into primary and secondary forms. The primary form is associated with abnormal variants in certain genes. At least four different genes have been identified including PRF1, UNC13D, STX11, and STXBP2. Primary HLH is mainly seen in children and is typically caused by defective natural killer cells and cytotoxic T-cells with various defects in the perforin–granzyme cell-death pathway. Secondary HLH develops because of a heightened, abnormal immune response that occurs due to a

trigger, such as infection, an autoimmune disorder, a weakened or depressed immune system, metabolic disorders, or cancer. It is much more common in adults.

- Diagnosis of HLH depends on if the patient is thought to have primary or secondary disease. In cases where signs and symptoms of disease are present in the absence of a trigger, the disease can be diagnosed one of three ways: genetic testing, cellular analysis of lymphocytes, and clinical symptoms and routine laboratory findings. Biallelic combination of large deletions, nonsense variants, and other previously well-described disease-causing genetic aberrations in HLH-associated genes are sufficient for primary HLH diagnosis. In patients carrying rare coding variants in HLH-associated genes that are novel, deemed likely pathogenic, of unknown significance, or conflicting interpretation, assays of lymphocyte cytotoxic function are strongly recommended. In individuals for whom biallelic possible disease-causing variants are not identified but who suffer repeated episodes of HLH, cellular diagnostic pathways assessing cytotoxic lymphocyte function are strongly recommended to rule out pathogenic non-coding aberrations. Cellular analysis showing absent perforin expression or defective cytotoxic lymphocyte exocytosis is strongly suspicious of primary HLH. The definitions of defective, low, impaired, and normal for cellular analysis are specific for each laboratory and cannot be generalized. Both the genetic and cellular analysis pathways of diagnosis require signs and symptoms of HLH for patients to be considered positive for the disease. Both primary and secondary HLH can be diagnosed via clinical symptoms and routine laboratory findings. Diagnosis via this pathway requires patients to meet 5 of the following criteria: fever greater than or equal to $38.5^{O}C$; splenomegaly; cytopenias affecting greater than or equal to 2 of 3 lineages in the peripheral blood including hemoglobin less than 90 g/L (in infants less than 4 weeks of age, hemoglobin less than 100 g/L), platelets less than 100 x 10^{9}/L, and/or neutrophils less than 1.0 x 10^{9}/L; hypertriglyceridemia and/or hypofibrinogenemia; hemophagocytosis in the bone marrow, spleen, or lymph nodes; ferritin greater than or equal to 500 µg/L; and/or soluble CD25 greater than or equal 2,400 U/mL. It is always of vital importance to search for the underlying cause of HLH.

- Prompt recognition and urgent treatment of HLH are critical for optimal outcomes. In some cases, emergency treatment must be initiated even before all diagnostic criteria are met. A critical goal of treatment is to urgently suppress life threatening inflammation by destroying immune cells. Treatment of HLH is stratified according to the patient's clinical status and is informed by the cause and/or triggering factor. Managing the triggering event can reduce the stimulus for immune activation.

- Patients with HLH gene mutations, hematologic malignancy, relapsing symptoms on or off therapy, and/or central nervous system disease will require hematopoietic stem cell transplant (HSCT). Because the response to therapy is not known at the time therapy is started, all patients and appropriate family members should undergo HLA typing to facilitate identification of an HSCT donor. Early initiation of HLA typing and selection of a donor shortens the pretransplantation interval, potentially improving the likelihood of survival.

- Patients who are clinically stable and have a condition responsible for triggering HLH may respond to treatment of the triggering condition alone. The major triggering conditions are infection, rheumatologic conditions, and lymphoid malignancies. A search for these conditions can be undertaken in clinically stable patients provided that the patient's status does not deteriorate. For patients with hematologic malignancies, HLH should be treated with HLH-specific therapy, followed by appropriate chemotherapy for the malignancy; often hematopoietic cell transplant will also be required. Infection should be diagnosed rapidly, and empiric antibiotic, antifungal, antiviral, or antiparasitic therapy should be initiated depending on the suspected organism. Patients who are clinically stable and respond within two to three days to treatment of the infection may be able to avoid HLH-specific chemotherapy. However, initiation of HLH-specific therapy for severely ill patients should not be delayed while awaiting resolution of a system infection. Some patients with an underlying condition that causes immunosuppression or disrupts immune homeostasis will respond to disease-specific therapy. If a patient with a rheumatologic condition is stable enough to delay HLH-

specific therapy, they can be treated with a course of corticosteroids and/or other therapy for the underlying condition.

- Patients with HLH who have deteriorating organ function should be treated immediately with HLH-specific treatment. Treatment should not be delayed while awaiting genetic or specialized immunologic testing. The HLH-94 protocol recommends eight weeks of induction therapy with etoposide and dexamethasone, with intrathecal hydrocortisone and methotrexate for those with central nervous system (CNS) involvement. Intrathecal therapy is continued until at least one week after CNS involvement has resolved, based on both clinical and CSF analysis.

- The response to initial therapy is a major factor in determining the need for additional therapy including HSCT. Response to induction therapy is monitored by assessing the patient clinically and using HLH disease-specific markers. Daily physical examination, complete blood count, coagulation tests, liver function, renal function, soluble IL-2 receptor alpha, CXCL9, and IL-18 should be completed. HSCT is indicated for those who do not fully recover by the end of the initial eight weeks of induction chemotherapy. Etoposide and dexamethasone therapy should be continued until HSCT is performed. Following HSCT, patients need to be monitored for disease recurrence, graft rejection, and HSCT complications.

- Some patients are intolerant of initial therapy for HLH, while others have disease that is refractory to initial treatment or progresses as induction therapy is being tapered, after having achieved remission, or while awaiting HSCT. Relapsed or refractory HLH may be manifest as clinical deterioration. Gamifant is an interferon gamma (IFNγ) blocking antibody indicated for the treatment of adult and pediatric patients with primary HLH with refractory, recurrent, or progressive disease or intolerance with conventional HLH therapy.

- Safety and efficacy of Gamifant for primary HLH was studied in the NI-0501-04 trial, a multicenter, open-label, single-arm phase II/III study of 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. Patients were diagnosed with primary HLH based on a molecular diagnosis, family history consistent with primary HLH, or by meeting five out of the 8 clinical symptoms or laboratory findings. Patients also had to fulfill one of the following criteria as assessed by the treating physician: having not responded or not achieved a satisfactory response or not maintained a satisfactory response to conventional HLH therapy or intolerance to conventional HLH treatments. 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 an unsatisfactory response. The primary endpoint was 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, central nervous system symptoms, complete blood count, fibrinogen and/or D-dimer, ferritin, and soluble CD25 (also referred to as soluble interleukin-2 receptor) levels. Complete response was defined as normalization of all HLH abnormalities. Partial response was defined as normalization of greater than or equal to 3 HLH abnormalities. HLH improvement was defined as greater than or equal to 3 HLH abnormalities improved by at least 50% from baseline. The primary endpoint was achieved with 63% of patients (p-value = 0.013) demonstrating an overall response at the end of treatment.

- Hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS)

  - Macrophage activation syndrome (MAS) is a form of secondary HLH occurring as a life-threatening complication of rheumatic diseases. It is most frequent in systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD), affecting about 10%–20% of patients. Similar to other forms of HLH, MAS is caused by excessive activation and expansion of T-lymphocytes and macrophages resulting in

hyperinflammation. MAS is characterized by fever, hepatosplenomegaly, cytopenias, liver dysfunction, coagulation abnormalities, and hyperferritinaemia. It may progress to multiple organ failure with mortality rates of 10%–20%.

- The European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) came up with diagnostic guidelines for MAS complicating systemic juvenile idiopathic arthritis in 2016. The criteria require that patients have ferritin greater than 684 ng/mL and any 2 of the following: platelet count less than or equal to 181 x 10^9/L, aspartate aminotransferase (AST) greater than 48 U/L, triglycerides greater than 156 mg/dL, or fibrinogen less than or equal to 360 mg/dL.

- Patients who are clinically stable and have a condition responsible for triggering HLH/MAS may respond to treatment of the triggering condition alone. Rheumatologic conditions are the major triggering conditions of HLH/MAS. A search for these conditions, if necessary, can be undertaken in clinically stable patients provided that the patient's status does not deteriorate. Some patients with an underlying condition that causes immunosuppression or disrupts immune homeostasis will respond to disease-specific therapy. If a patient with a rheumatologic condition is stable enough to delay HLH/MAS-specific therapy, they can be treated with a course of corticosteroids and/or other therapy for the underlying condition.

- Patients with HLH/MAS who have deteriorating organ function should be treated immediately with HLH/MAS-specific treatment. Treatment should not be delayed while awaiting genetic or specialized immunologic testing. The 2022 EULAR/ACR task force recommends use of glucocorticoids, anakinra, and/or intravenous immunoglobulin (IVIG) for empiric immunomodulation in suspected HLH/MAS. Multiple treatments may be initiated concurrently depending on clinical context and availability. Published treatment data demonstrate the strongest support for glucocorticoids across all forms of HLH/MAS. The choice of glucocorticoid formulation and route of administration should be tailored to the patient and care setting. Pulse doses of intravenous methylprednisolone, 10 – 30 mg/kg/day up to 1 g given daily, are effective in severe rheumatic diseases and have been used successfully in HLH/MAS.

- The response to initial therapy is a major factor in determining the need for additional therapy. Response to induction therapy should be monitored closely for evidence of improvement in their temperature, physical examination, such as rash, lymphadenopathy, and organ-specific findings, and laboratory abnormalities, such as cytopenias, transaminitis, and hyperferritinemia. IL-18 and CXCL9 levels can be helpful in the diagnosis and monitoring of HLH/MAS, although IL-18 may remain persistently elevated in patients with inactive disease. Since all of the initial treatments have a relatively quick onset of action, some improvement in clinical and laboratory features should be seen within a few days of initiating therapy.

- Some patients are intolerant of initial therapy for HLH/MAS, while others have disease that is refractory to initial treatment or progresses as induction therapy is being tapered or after having achieved remission. Relapsed or refractory HLH/MAS may be manifest as clinical deterioration. Gamifant is an interferon gamma (IFNγ) blocking antibody indicated for the treatment of adult and pediatric patients with HLH/MAS in known or suspected Still's disease, including sJIA, with an inadequate response or intolerance to glucocorticoids, or with recurrent MAS.

- Safety and efficacy of Gamifant for HLH/MAS was studied in the NI-0501-14 and NI-0501-06 trials, two open-label, single arm, multicenter studies of 39 patients with confirmed or suspected HLH/MAS in Still's disease, including sJIA, with an inadequate response to high-dose glucocorticoid treatment.. Patients were diagnosed with HLH/MAS if they had a ferritin level greater than 684 ng/mL and any 2 of the following: platelet count less than or equal to 181×10^9/L, AST greater than 48 U/L, triglycerides greater than 156 mg/dL, or fibrinogen levels less than or equal to 360 mg/dL. High-dose glucocorticoids were defined as greater than or equal to 2 mg/kg/day of prednisone equivalent in two divided doses, or at least 60 mg/day in patients weighing 30 kg or more, including but not limited to pulses up to 30 mg/kg/day for at least 3

consecutive days. All patients received an initial starting dose of Gamifant of 6 mg/kg on day 0, followed by 3 mg/kg every 3 days until day 15 and twice weekly until day 28. Treatment with Gamifant could be stopped on investigator's assessment of remission, but not before three Gamifant doses have been administered. Frequency between infusions could be shortened, dose could be increased or treatment prolonged on investigator's assessment of unsatisfactory response. The primary endpoint was HLH/MAS remission by week 8 defined as resolution of clinical signs and symptoms according to the physician global assessment and white blood cell and platelet count above the lower limit of normal, lactate dehydrogenase (LDH), alanine aminotransferase and aspartate aminotransferase below 1.5 times upper limit of normal (ULN), fibrinogen greater than 100 mg/dL and ferritin levels decreased by at least 80% or below 2000 ng/mL, whichever was lower. The primary endpoint was achieved with 53.8% of patients (95% CI: 37.2, 69.9).

References:

1. Gamifant [prescribing information]. Waltham, MA: Sobi Inc.; June 2025.
2. Henter JI. Hemophagocytic lymphohistiocytosis. NEJM. 2025 Feb 5; 392: 584 – 98.
3. National Organization of Rare Disorders. Hemophagocytic lymphohistiocytosis. 2016 Dec 13. Available at: https://rarediseases.org/rare-diseases/hemophagocytic-lymphohistiocytosis/. Accessed on May 28, 2025.
4. Henter JI, Sieni E, Eriksson J, et al. Diagnostic guidelines for familial hemophagocytic lymphohistiocytosis revisited. Blood. 2024 Nov 28; 144 (22): 2308 – 18.
5. Bergsten E, Horne AC, Aricó M, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. Blood. 2017 Sep 21; 130 (25): 2728 – 38.
6. Henter JI, Aricò M, Egeler RM, et al. HLH-94: a treatment protocol for hemophagocytic lymphohistiocytosis. HLH study Group of the Histiocyte Society. Med Pediatr Oncol. 1997; 28: 342.
7. Locatelli F, Jordan MB, Allen C, et al. Emapalumab in children with primary hemophagocytic lymphohistiocytosis. NEJM. 2020 May 7; 382 (19): 1811 - 22.
8. Clinicaltrials.gov. Evaluate efficacy, safety and tolerability, PK and PD of emapalumab in children and adults with MAS in Still's or SLE. Available at: https://clinicaltrials.gov/study/NCT05001737#participation-criteria. Accessed on June 30, 2025.
9. De Benedetti F, Grom AA, Brogan PA, et al. Efficacy and safety of emapalumab in macrophage activation syndrome. Ann Rheum Dis. 2023 Jun; 82 (6): 857 - 65.
10. Ravelli A, Minoia F, Davl S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. Arth Rheum. 2016 March; 68 (3): 566 – 76.
11. Shakoory B, Geerlinks A, Wilejto M, at al. The 2022 EULAR/ACR points to consider at the early stages of diagnosis and management of suspected haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS). Ann Rheum Dis. 2023; 82: 1271 - 85.

<table>
<tr><th colspan="3">Policy History</th></tr>
<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>1.1</td><td>Effective Date:
09/03/2025</td><td>UM medical management system update for BCBS and BCN
<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>Yes</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>No</td></tr><tr><td>BCNA</td><td>No</td></tr></table></td></tr>
<tr><td>1.0</td><td>P&T Date:
08/07/2025

Effective Date:
09/22/2025</td><td>New Policy
<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>No</td></tr><tr><td>BCN</td><td>No</td></tr><tr><td>MAPPO</td><td>No</td></tr><tr><td>BCNA</td><td>No</td></tr></table></td></tr>
</table>

** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*