Gamifant® (Emapalumab-Lzsg)

Policy Number: 2025D0077J
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Community Plan Policy

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Coverage Rationale

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Gamifant is proven for the treatment of primary hemophagocytic lymphohistiocytosis (HLH) in patients who meet all of the following criteria:

- Diagnosis of primary hemophagocytic lymphohistocytosis; **and**
- Patient has refractory, recurrent or progressive disease, or intolerance with conventional HLH therapy (e.g., etoposide, corticosteroids, cyclosporine, anti-thymocyte globulin, methotrexate); **and**
- Dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Authorization will be for no more than 6 months

Gamifant is medically necessary for the treatment of primary hemophagocytic lymphohistiocytosis (HLH) in patients who meet all of the following criteria:

- Submission of medical records (e.g., chart notes, laboratory values) confirming **one** the following:
  - Confirmation of a gene mutation known to cause primary HLH (e.g., PRF1, UNC13D, RAB27A, STX11, STXBP2); **or**
  - Confirmation that **five** of the following clinical characteristics are present:
    - Fever
    - Splenomegaly
    - **Two** of the following cytopenias in the peripheral blood:
      - Hemoglobin < 9 g/dL; **or**
      - Platelet count < 100 x 109/L; **or**
      - Neutrophils < 1 x 109/L
    - **One** of the following:
      - Hypertriglyceridemia defined as fasting triglycerides ≥ 3 mmol/L or ≥ 265 mg/dL; **or**
      - Hypofibrinogenemia defined as fibrinogen ≤ 1.5 g/L
    - Hemophagocytosis in bone marrow, spleen, or lymph nodes with no evidence of malignancy
    - Low or absent natural killer cell activity
    - Ferritin ≥ 500 mcg/L
    - Soluble CD25 (i.e., soluble IL-2 receptor) ≥ 2,400 U/mL

  and
- Patient has refractory, recurrent or progressive disease, or intolerance with conventional HLH therapy (e.g., etoposide, corticosteroids, cyclosporine, anti-thymocyte globulin, methotrexate); **and**
- Gamifant will be administered with dexamethasone; **and**

- Patient is a candidate for hematopoietic stem cell transplant; **and**
- Gamifant is being used as part of the induction or maintenance phase of hematopoietic stem cell transplant, which is to be discontinued at the initiation of conditioning for stem cell transplant; **and**
- Dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Authorization will be for no more than 6 months

Gamifant is proven for the treatment of hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS) in patients who meet all of the following criteria:

- **Initial Therapy**
  - Diagnosis of hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS); **and**
  - Known or suspected diagnosis of Still's disease, including systemic juvenile idiopathic arthritis (sJIA); **and**
  - Inadequate response or intolerance to glucocorticoids; **and**
  - Dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
  - Approval is for no more than 12 months
- **Continuation of Therapy**
  - Documentation of a positive clinical response to Gamifant; **and**
  - Dosing is in accordance with the FDA approved labeling; **and**
  - Reauthorization will be for no more than 12 months

Gamifant is medically necessary for the treatment of hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS) in patients who meet all of the following criteria:

- **Initial Therapy**
  - Submission of medical records (e.g., chart notes, laboratory values) confirming the following:
    - Confirmed or suspected diagnosis of systemic juvenile idiopathic arthritis (sJIA) or adult onset Still's disease (AOSD); **and**
    - Diagnosis of active MAS with **both** of the following:
      - Ferritin > 684 ng/mL
      - **Two** of the following laboratory criteria:
        - Platelet count ≤ 181 x 10^9/L; **or**
        - AST > 48 U/L
        - Triglycerides > 156 mg/dL
        - Fibrinogen level ≤ 360 mg/dL

    and
  - Patient has had an inadequate response to high-dose intravenous glucorticoids; **and**
  - Dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
  - Initial authorization will be for no more than 12 months
- **Continuation of Therapy**
  - Documentation of a positive clinical response to Gamifant; **and**
  - Dosing is in accordance with the FDA approved labeling; **and**
  - Reauthorization will be for no more than 12 months

Gamifant is not proven or medically necessary for the treatment of secondary HLH.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

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

Diagnosis Code	Description
D76.1	Hemophagocytic lymphohistiocytosis
D76.2	Hemophagocytic syndrome, infection-associated
D76.3	Other histiocytosis syndromes

Background

Primary hemophagocytic lymphohistiocytosis is a rare syndrome with an estimated incidence of around 1:50,000 live-births characterized by immune dysregulation and hyperinflammation. It typically manifests in infancy and is associated with high mortality. Macrophage activation syndrome (MAS), a form of HLH, is a severe complication of rheumatic diseases, occurring most frequently in Still's disease, including systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease.

Emapalumab is a monoclonal antibody that binds to interferon gamma (IFNγ) and neutralizes it. Nonclinical data suggest that IFNγ is involved in HLH by being hypersecreted. Emapalumab decreases plasma concentrations of CXCL9, a chemokine induced by IFNγ.

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

Clinical Evidence

Hemophagocytic Lymphohistiocytosis

The efficacy of emapalumab in the treatment of HLH was assessed in study NI-0501-04, a phase 2/3, open-label, single-arm, multicenter clinical trial (NCT01818492). The study was designed to study the pharmacokinetics, efficacy, and safety of emapalumab in pediatric patients with suspected or confirmed primary HLH who were treatment naive or had not responded to or were intolerant to standard HLH therapy. In the study, patients were treated for up to 8 weeks, but not less than 4 weeks based on patient condition and donor availability for hematopoietic stem cell transplantation. Initially, emapalumab was dosed 1mg/kg every three days until day 15, when it was administered twice weekly thereafter. Dose increases were allowed, up to 10mg/kg/day and dexamethasone was administered to study patients as well. The primary efficacy endpoint was overall response at the end of treatment, defined as achievement of either a complete or partial response or HLH improvement using protocol-specified criteria. Secondary efficacy endpoints included measures of the sustained control of HLH disease so that patients could receive hematopoietic stem cell transplantation as well as survival. Overall, 64.7% of study patients had an overall response at end of treatment. Overall, 88.2% of patients responded to emapalumab treatment, with disease control occurring shortly after initiation of emapalumab treatment, with a median time to first response of 8 days. Overall, 65% of patients underwent hematopoietic stem cell transplantation, with engraftment rates of 86.4%. Post hematopoietic stem cell transplantation event-free survival was 81.8%.

Study NI-0501-05, was a multicenter follow-up study to collect safety and outcome data for patients who received emapalumab through NI-0501-04 and compassionate use programs (NCT02069899). Patients were followed for 1 year after hematopoietic stem cell transplantation or after the last infusion of emapalumab for patients in whom hematopoietic stem cell transplantation was not performed. The most commonly reported adverse events in the NI-0501-04/05 studies during the pre-conditioning phase included bacterial, fungal, and viral infections (56%) and aggravated condition aggravated (50.0%), which includes HLH reactivation, flare, worsening. Other commonly reported AEs during the pre-conditioning period included hypertension (41.2%), infusion-related reactions (27%), and pyrexia (24%). In addition, 56% of patients in the NI-0501-04/-05 studies reported infections during the preconditioning period. During the post-conditioning period, the most commonly reported adverse events were pyrexia (52.2%) and hypertension (43.5%), along with common hematopoietic stem cell transplantation complications. As of July 20, 2017, 20 of 51 patients receiving drug through compassionate use programs and the NI-0501-04/05 studies had fatal adverse events. The fatal adverse events were reported to be consistent with complications of HLH, rather than being related to treatment with emapalumab. Regarding serious adverse events, the most common ones reported during the pre-conditioning period were aggravated HLH (18.9%) and respiratory failure (9.4%). Common serious adverse events after hematopoietic stem cell transplantation included condition aggravated and engraft failure (11.1% each), and pyrexia, acute GVHD in intestine, engraftment syndrome, *Klebsiella* sepsis, and septic shock (7.4% each). Adverse events resulting in treatment withdrawal included disseminated histoplasmosis and HLH worsening. Additionally, in the NI-0501-04/05 studies, necrotizing fasciitis and disseminated histoplasmosis have been reported to be related to emapalumab.

Henter et al. completed HLH-2004 as a follow up to HLH-94, the first prospective international treatment study for hemophagocytic lymphohistiocytosis (HLH), where diagnosis was based on five criteria which included fever,

splenomegaly, bicytopenia, hypertriglyceridemia and/or hypofibrinogenemia, and hemophagocytosis. In HLH-2004 three additional criteria were added and include low/absent NK-cell-activity, hyperferritinemia, and high-soluble interleukin-2-receptor levels. For diagnosis, five of these eight criteria must be fulfilled, unless a family history or genetic test is consistent with HLH. HLH-2004 chemo-immunotherapy includes initial treatment with etoposide, dexamethasone, & cyclosporine and intrathecal therapy with methotrexate and corticosteroids in select patients. Subsequent hematopoietic stem cell transplantation is recommended for patients with familial disease or molecular diagnosis, and patients with severe and persistent, or reactivated disease.

Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome

The efficacy of emapalumab was evaluated in two open-label, single arm, multicenter studies which enrolled a total of 39 patients with hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS) in Still's disease, including systemic Juvenile Idiopathic Arthritis (sJIA), with an inadequate response to high-dose glucocorticoid treatment. In each study, patients were required to fulfill the following criteria for enrollment: confirmed or suspected diagnosis of sJIA or AOSD; a diagnosis of active MAS with ferritin > 684 ng/mL and any 2 of these 4 laboratory criteria: platelet count ≤ 181×109 /L, AST > 48 U/L, triglycerides > 156 mg/dL, or fibrinogen levels ≤ 360 mg/dL; an inadequate response to high-dose IV glucocorticoids. In each study, emapalumab was administered at an initial dose of 6 mg/kg, followed by at least 3 mg/kg every 3 days until Day 16, and then twice weekly thereafter. The pooled analysis included all patients from Study NI-0501-06 (NCT 03311854) and Study NI-0501-14 (NCT05001737). These two studies enrolled 39 patients who received emapalumab, and 37 patients completed the studies (95%). The efficacy of emapalumab was based on complete response (CR), a composite endpoint consisting of clinical resolution of MAS signs and symptoms [a visual analogue scale (VAS), of ≤ 1 cm (range 0 to 10 cm)] and the following 7 laboratory parameter endpoints: WBC count and platelet count above the lower limit of normal (LLN), LDH, AST and ALT below 1.5×the upper limit of normal (ULN), fibrinogen > 100 mg/dL, and ferritin levels decreased ≥ 80% from values at screening or baseline (whichever was higher) or < 2000 ng/mL, whichever was lower. Complete response was achieved in 53.8% (95% CI: 37.2, 69.9). The most common adverse reactions (≥ 20%) with Gamifant use in patients with HLH/MAS in Still's disease were viral infections, including cytomegalovirus infection or reactivation, and rash.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Gamifant (emapalumab-lzsg) is an interferon gamma (IFNγ) neutralizing antibody indicated 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.

Gamifant is also indicated for the treatment of adult and pediatric (newborn and older) patients with HLH/macrophage activation syndrome (MAS) in known or suspected Still's disease, including systemic Julvenile Idiopathic Arthritis (sJIA), with an inadequate response or intolerance to glucocorticoids, or with recurrent MAS.

References

1. Gamifant [package insert]. Stockholm, Sweden: Sobi, Inc.; June 2025.
2. Henter JI, Horne A, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48:124-31.
3. Locatelli F, Jordan MB, Allen C, et al. Emapalumab in Children with Primary Hemophagocytic Lymphohistiocytosis. n Engl J Med. 2020;382(19):1811-1822.

Policy History/Revision Information

Date	Summary of Changes

10/01/2025	**Coverage Rationale**
	Hemophagocytic Lymphohistiocytosis (HLH)
	• Added coverage criteria for proven indications requiring:
	  ○ Diagnosis of primary hemophagocytic lymphohistiocytosis
	  ○ Patient has refractory, recurrent or progressive disease, or intolerance with conventional hemophagocytic lymphohistiocytosis (HLH) therapy (e.g., etoposide, corticosteroids, cyclosporine, anti-thymocyte globulin, methotrexate)

Date	Summary of Changes
	○ Dosing is in accordance with the U.S. Food and Drug Administration (FDA) approved labeling ○ Authorization will be for no more than 6 months • Revised medical necessity criteria; replaced criterion requiring: ○ "Confirmation of a gene mutation known to cause primary HLH (e.g., PRF1, UNC13D)" with "confirmation of a gene mutation known to cause primary HLH (e.g., PRF1, UNC13D, *RAB27A, STX11, STXBP2*)" ○ "Confirmation of fever ≥ *101.3°F*" with "confirmation of fever" ○ "Confirmation of low or absent natural killer cell activity *(according to local laboratory reference)*" with "confirmation of low or absent natural killer cell activity" ○ "The patient has refractory, recurrent, or progressive disease, or intolerance with conventional HLH therapy (*i.e., etoposide + dexamethasone*)" with "the patient has refractory, recurrent, or progressive disease, or intolerance with conventional HLH therapy (*e.g., etoposide, corticosteroids, cyclosporine, anti-thymocyte globulin, methotrexate*)" ○ "*Approval is* for no more than 6 months" with "*authorization will be* for no more than 6 months" • Replaced references to "stem cell transplant" with "*hematopoietic* stem cell transplant" ***Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS)*** • Added language to indicate: ○ Gamifant is proven for the treatment of HLH MAS in patients who meet all of the following criteria: Initial Therapy ▪ Diagnosis of hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS) ▪ Known or suspected diagnosis of Still's disease, including systemic juvenile idiopathic arthritis (sJIA) ▪ Inadequate response or intolerance to glucocorticoids ▪ Dosing is in accordance with the U.S. FDA approved labeling ▪ Approval is for no more than 12 months Continuation of Therapy ▪ Documentation of a positive clinical response to Gamifant ▪ Dosing is in accordance with the U.S. FDA approved labeling ▪ Reauthorization will be for no more than 12 months ○ Gamifant is medically necessary for the treatment of HLH MAS in patients who meet all of the following criteria: Initial Therapy ▪ Submission of medical records (e.g., chart notes, laboratory values) confirming the following: – Confirmed or suspected diagnosis of systemic juvenile idiopathic arthritis (sJIA) or adult onset Still's disease (AOSD) – Diagnosis of active MAS with both of the following: • Ferritin > 684 ng/mL • Two of the following laboratory criteria: platelet count ≤ 181 x 10^9/L, AST > 48 U/L, triglycerides > 156 mg/dL, fibrinogen level ≤ 360 mg/dL ▪ Patient has had an inadequate response to high-dose intravenous glucocorticoids ▪ Dosing is in accordance with the U.S. FDA approved labeling ▪ Initial authorization will be for no more than 12 months Continuation of Therapy ▪ Documentation of a positive clinical response to Gamifant ▪ Dosing is in accordance with the U.S. FDA approved labeling ▪ Reauthorization will be for no more than 12 months **Applicable Codes** • Added ICD-10 diagnosis codes D76.2 and D76.3 **Supporting Information** • Updated *Background*, *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information

Date	Summary of Changes
	• Archived previous policy version 2024D0077I

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.