

# Gamifant® (Emapalumab-Lzsg) (for Louisiana Only)

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[Instructions for Use](#)

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## Application

This Medical Benefit Drug Policy only applies to the state of Louisiana.

## Coverage Rationale

Emapalumab is proven and medically necessary for the treatment of primary hemophagocytic lymphohistiocytosis (HLH) in patients who meet all of the following criteria:<sup>1-4</sup>

- 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  $\geq 101.3^{\circ}\text{F}$
    - Splenomegaly
    - **Two** of the following cytopenias in the peripheral blood:
      - Hemoglobin  $< 9$  g/dL; **or**
      - Platelet count  $< 100 \times 10^9/\text{L}$ ; **or**
      - Neutrophils  $< 1 \times 10^9/\text{L}$
    - **One** of the following:
      - Hypertriglyceridemia defined as fasting triglycerides  $\geq 3$  mmol/L or  $\geq 265$  mg/dL; **or**
      - Hypofibrinogenemia defined as fibrinogen  $\leq 1.5$  g/L
    - Hemophagocytosis in bone marrow, spleen, or lymph nodes with no evidence of malignancy
    - Low or absent natural killer cell activity ([according to local laboratory reference](#))
    - Ferritin  $\geq 500$  mcg/L
    - Soluble CD25 (i.e., soluble IL-2 receptor)  $\geq 2,400$  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](#); ~~e.g., etoposide + dexamethasone~~); **and**
- Emapalumab will be administered with dexamethasone; **and**
- Patient is a candidate for [hematopoietic](#) stem cell transplant; **and**
- Emapalumab 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**
- ~~Approval is~~ [Authorization will be](#) for no more than 6 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  $\leq 181 \times 10^9/L$ ; or
        - AST > 48 U/L
        - Triglycerides > 156 mg/dL
        - Fibrinogen level  $\leq 360$  mg/dL
- and**
- Patient has had an inadequate response to high-dose intravenous glucocorticoids; **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

Emapalumab 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 federal, state, or contractual requirements 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.

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

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

## 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 (IFN $\gamma$ ) and neutralizes it. Nonclinical data suggest that IFN $\gamma$  is involved in HLH by being hypersecreted. Emapalumab decreases plasma concentrations of CXCL9, a chemokine induced by IFN $\gamma$ .

### **Hemophagocytic Lymphohistiocytosis**

The efficacy of emapalumab in the treatment of HLH was assessed in study NI-0501-04, a phase 2-3, open-label, multicenter, 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%.<sup>3,5</sup>

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.<sup>3-5</sup>

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.<sup>2</sup>

### **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  $\leq 181 \times 10^9$  /L, AST >48 U/L, triglycerides >156 mg/dL, or fibrinogen levels  $\leq 360$  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 1.5xthe 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 is an interferon gamma (IFN $\gamma$ ) 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.<sup>1</sup>

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 Juvenile Idiopathic Arthritis (sJIA), with an inadequate response or intolerance to glucocorticoids, or with recurrent MAS.

References

1. Gamifant [package insert]. Stockholm, Sweden: Sobi, Inc.; ~~July 2024~~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.

~~2-3. Locatelli F, Jordan MB, Allen C, et al. Emapalumab in Children with Primary Hemophagocytic Lymphohistiocytosis. N Engl J Med. 2020;382(19):1811-1822.~~

3. ~~Study NI-0501-04. Data on file, Sobi Pharmaceuticals.~~

4. ~~Study NI-0501-05. Data on file, Sobi Pharmaceuticals.~~

5. ~~Henter JI, von Bahr Greenwood T, Bergsten E. Emapalumab in Primary Hemophagocytic Lymphohistiocytosis. N Engl J Med. 2020;383(6):596-598.~~

Policy History/Revision Information

Date	Summary of Changes
<u>TBD</u>	<u>Annual review. Expanded 'is proven' criteria for HLH. Updated examples of gene mutations and conventional treatment within 'medical necessity' criteria for HLH. Added criteria for new indication, HLH/MAS. Updated Applicable Codes, Background, Clinical Evidence, FDA section, and References.</u>

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. 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.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The 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.

## Archived Policy Versions

Effective Date	Policy Number	Policy Title
12/01/2023 – 11/30/2024	CSLA2023D0077G	<a href="#">Gamifant® (Emapalumab-Lzsg) (for Louisiana Only)</a>
12/01/2022 – 11/30/2023	CSLA2022D0077F	<a href="#">Gamifant® (Emapalumab-Lzsg) (for Louisiana Only)</a>
02/01/2021 – 11/30/2022	CSLA2021D0077E	<a href="#">Gamifant® (Emapalumab-Lzsg) (for Louisiana Only)</a>
10/01/2019 – 01/31/2021	CSLA2019D0077D	<a href="#">Gamifant® (Emapalumab-Lzsg) (for Louisiana Only)</a>
07/01/2019 – 09/30/2019	CS2019D0077C	<a href="#">Gamifant™ (Emapalumab-Lzsg)</a>
03/01/2019 – 06/30/2019	CS2019D0077B	<a href="#">Gamifant™ (Emapalumab-Lzsg)</a>
02/01/2019 – 02/28/2019	CS2019D0077A	<a href="#">Gamifant™ (Emapalumab-Lzsg)</a>