# Medical Drug Clinical Criteria

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| **Subject:** | Gamifant (emapalumab-lzsg) | | |
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| **Status:** | Revised | **Last Review Date:** | 05/19/2023 |

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## Overview

This document addresses the use of Gamifant (emapalumab-lzsg), an interferon gamma (IFNγ) blocking antibody approved for the treatment of individuals with refractory primary hemophagocytic lymphohistiocytosis (HLH).

HLH is a rare, life-threatening hyperinflammatory condition caused by a highly stimulated but ineffective immune response. HLH comprises two different conditions that may be difficult to distinguish from one another: a primary (genetic) and secondary (acquired) form. Primary HLH, otherwise known as familial hemophagocytic lymphohistiocytosis, refers to HLH caused by a gene mutation and is usually diagnosed within the first year of life. Secondary HLH can occur at any age and is generally triggered by another condition such as severe infections, malignancies, rheumatologic disorders, or metabolic diseases. Despite advances in molecular diagnosis it remains difficult to distinguish between primary and secondary forms of HLH as both can be triggered by infections or other immune activating events and gene mutations can be found in individuals of any age or with any family history.

HLH is predominately associated with fever and cytopenias and progressive tissue damage from hyperinflammation can lead to organ failure. The Histiocyte Society developed a protocol for the diagnosis and treatment of HLH (HLH-94), which was updated in 2004 (HLH-2004). Per HLH-2004, a diagnosis may be established if an individual has a molecular diagnosis consistent with HLH or meets five of the following eight criteria: (1) fever, (2) splenomegaly, (3) cytopenias affecting 2 of 3 lineages in the peripheral blood, (4) hypertriglyceridemia and/or hypofibrinogenemia, (5) hemophagocytosis in bone marrow, spleen, or lymph nodes with no evidence of malignancy, (6) low or absent NK-cell activity, (7) elevated ferritin, or (8) elevated soluble CD25. Reported mutations in the following genes are consistent with a molecular diagnosis of HLH: PRF, UNC13D, STX11, and STXBP2. Griscelli Syndrome type 2, X-linked lymphoproliferative disorder, and Chediak-Higashi syndrome can develop true HLH episodes during their clinical course and mutations associated with these disorders are also consistent with an HLH molecular diagnosis.

Prompt initiation of treatment is essential for survival, but a timely diagnosis can be challenging given the rarity of the condition, variable clinical presentation, and lack of specificity regarding clinical and laboratory findings. Diagnostic criteria may be too stringent to capture all individuals with HLH, therefore initiation of therapy is appropriate for individuals with a high degree of clinical suspicion for HLH even if they do not meet all diagnostic criteria elements. Treatment for primary HLH includes induction chemotherapy with etoposide and dexamethasone with or without cyclosporine generally followed by continuation therapy to control hyperinflammation until an individual undergoes hematopoietic stem cell transplantation (HSCT) which can be curative. Intrathecal methotrexate and hydrocortisone may be utilized in individuals with central nervous system involvement. Gamifant is approved for individuals with primary HLH who experienced refractory, recurrent, or progressive disease during conventional HLH therapy or who are intolerant of conventional HLH therapy.

The dose of Gamifant is titrated based on disease response. The initial dose is 1mg/kg, then can be increased based on the response outlined in the FDA prescribing information as shown in the box below[+]. After the patient's clinical condition is stabilized, decrease the dose to the previous level to maintain clinical response.

| Treatment Day | GAMIFANT Dose | Criteria for Dose Increase |
|---|---|---|
| Day 1 | Starting Dose of 1 mg/kg | N/A |
| On Day 3 | Increase to 3 mg/kg | Unsatisfactory improvement in clinical condition, as assessed by a healthcare provider AND at least one of the following:<br>• Fever – persistence or recurrence<br>• Platelet count<br>  ○ If baseline < 50,000/mm3 and no improvement to >50,000/mm3 |
| From Day 6 onwards | Increase to 6 mg/kg | |

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|---|---|---|
| | | ○ If baseline > 50,000/mm3 and less than 30% improvement<br>○ If baseline > 100,000/mm3 and decrease to < 100,000/mm3<br>• Neutrophil count<br>○ If baseline < 500/mm3 and no improvement to > 500/mm3<br>○ If baseline > 500 -1000/mm3 and decrease to < 500/mm3<br>○ If baseline 1000-1500/mm3 and decrease to < 1000/ mm3<br>• Ferritin (ng/mL)<br>○ If baseline ≥ 3000 ng/mL and < 20% decrease<br>○ If baseline < 3000 ng/mL and any increase to > 3000 ng/mL<br>• Splenomegaly – any worsening<br>• Coagulopathy (both D-Dimer and Fibrinogen must apply)<br>• D-Dimer<br>○ If abnormal at baseline and no improvement<br>• Fibrinogen (mg/dL)<br>○ If baseline levels ≤ 100 mg/dL and no improvement<br>○ If baseline levels > 100 mg/dL) and any decrease to < 100 mg/dL |
| From Day 9 onwards | Increase to 10 mg/kg | Assessment by a healthcare provider that based on initial signs of response, a further increase in GAMIFANT dose can be of benefit |

[+]Gamifant (emapalumab-lzsg) [prescribing information]. Waltham, MA; Sobi Inc; June 2020.

## Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

**Gamifant (emapalumab-lzsg)**

Requests for Gamifant (emapalumab-lzsg), may be approved if the following criteria are met:

I. Documentation is provided that individual has a diagnosis of active primary hemophagocytic lymphohistiocytosis (HLH) as confirmed by **one** of the following:
   A. Individual has a genetic mutation known to cause HLH; **OR**
   B. Individual has a family history consistent with primary HLH; **OR**
   C. Individual meets **five** of the following criteria:
      1. Fever
      2. Splenomegaly
      3. Cytopenias affecting 2 of 3 lineages in the peripheral blood (hemoglobin < 9 g/dL (or < 10 g/dL in infants), platelets < 100 x $10^9$/L, neutrophils < 1 x $10^9$/L)
      4. Hypertriglyceridemia (fasting TG ≥ 265 mg/dL) and/or hypofibrinogenemia (fibrinogen ≤ 1.5 g/L)
      5. Hemophagocytosis in bone marrow, spleen, or lymph nodes with no evidence of malignancy
      6. Low or absent NK-cell activity
      7. Ferritin ≥ 500 mcg/L
      8. Soluble CD25 ≥ 2400 U/mL;

**AND**

II. Individual is using in combination with dexamethasone; **AND**

III. Individual has had an inadequate response to, is intolerant of, or has a contraindication to conventional therapy (such as etoposide, dexamethasone, or cyclosporine); **AND**

IV. Individual is a candidate for hematopoietic stem cell transplant or has not received a successful hematopoietic stem cell transplant.

Continuation requests for Gamifant (emapalumab-lzsg) may be approved if the following criterion is met:

I. Individual has clinical response to treatment with Gamifant (improvement in initial clinical or laboratory parameters); **AND**
II. Documentation is provided that individual is experiencing residual active disease; **AND**
III. Documentation is provided that individual has not received a successful hematopoietic stem cell transplant; **AND**
IV. Dose has been titrated to the minimum dose and frequency necessary to achieve satisfactory improvement as defined by FDA labeling for Gamifant (emapalumab-lzsg).

Requests for Gamifant (emapalumab-lzsg) may not be approved for the following:

I. Individual has a diagnosis of secondary or acquired HLH; **OR**
II. Individual has not met all the above criteria or for all other indications.

**Approval duration:**
Initial Requests: 3 months
Continuation Requests: 6 months

## Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

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|---|---|
| **HCPCS** | |
| J9210 | Injection, emapalumab-lzsg, 1 mg [Gamifant] |
| **ICD-10 Diagnosis** | |
| D76.1 | Hemophagocytic lymphohistiocytosis |

## Document History

Reviewed: 05/19/2023
Document History:

- 05/19/2023 – Annual Review: No changes. Coding Reviewed: No changes.
- 05/20/2022 – Annual Review: Update Gamifant criteria for initial and continuation criteria, add approval duration, wording and formatting changes. Administrative update to add documentation. Coding Reviewed: No changes.
- 05/21/2021 – Annual Review: Wording and formatting changes. Coding Reviewed: No changes.
- 03/15/2021 – Annual Review: No changes. Coding changes. No changes.
- 03/16/2020 – Annual Review: No changes. Coding reviewed. No changes.
- 08/16/2019- Coding Reviewed: Added HCPCS code J9210 (Effective 10/1/19), Delete J3590, and C9050 (Effective 10/1/19)
- 06/25/2019- Coding Reviewed: Added HCPCS code C9050 (Effective 7/1/19), Delete C9399 (Effective 7/1/19)
- 02/22/2019 – Annual Review: Add new clinical criteria document for Gamifant. Coding update: Added C9399, J3590 for Gamifant and D76.1 ICD-10 dx.

## References


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3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2023; Updated periodically.
5. Henter JI, Horne AC, et al. HLH-2004: Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124–131.


Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.