Clinical Policy: Emapalumab-lzsg (Gamifant)

Reference Number: ERX.SPA.313
Effective Date: 03.01.19
Last Review Date: 02.22
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Emapalumab-lzsg (Gamifant™) is an interferon gamma (IFNγ) blocking antibody.

FDA Approved Indication(s)
Gamifant is 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.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Gamifant is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Primary Hemophagocytic Lymphohistiocytosis (must meet all)**:**

1. Diagnosis of primary HLH (i.e., familial (inherited) HLH);
2. Diagnosis is confirmed based on one of the following (a, b, or c):
   a. Genetic mutation known to cause HLH;
   b. Family history consistent with primary HLH;
   c. Five of the following criteria are satisfied (1-8):
      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 ≥ 3 mmol/L or ≥ 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 (sCD25; i.e. soluble IL-2 receptor) ≥ 2,400 U/mL;
3. Prescribed by or in consultation with a hematologist;
4. Failure of conventional HLH therapy that includes an etoposide- and dexamethasone-based regimen, unless contraindicated or clinically significant adverse effects are experienced;
5. Documentation of a scheduled bone marrow or hematopoietic stem cell transplantation (HSCT) or identification of a transplant donor is in process;
6. Dose does not exceed 10 mg/kg per dose, two doses per week.

Approval duration: 2 months

B. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Primary Hemophagocytic Lymphohistiocytosis (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy – including but not limited to improvement in any of the following parameters:
   a. Fever reduction;
   b. Splenomegaly;
   c. Central nervous system symptoms;
   d. Complete blood count;
   e. Fibrinogen and/or D-dimer;
   f. Ferritin;
   g. Soluble CD25 (also referred to as soluble interleukin-2 receptor) levels;
3. If request is for a dose increase, new dose does not exceed 10 mg/kg per dose, two doses per week.

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
HLH: hemophagocytic lymphohistiocytosis
HSCT: hematopoietic stem cell transplantation

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
etoposide (Toposar®)	150 mg/m^2 IV twice weekly for 2 weeks and then weekly for an additional 6 weeks. Continuation therapy from week 9 until HSCT: 150 mg/m^2 every alternating second week	150 mg/m^2 per dose
dexamethasone	10 mg/m^2 PO or IV for 2 weeks followed by 5 mg/m^2 for 2 weeks, 2.5 mg/m^2 for 2 weeks, 1.25 mg/m^2 for 1 week, and 1 week of tapering Continuation therapy from week 9 until HSCT: 1010 mg/m^2 for 3 days every second week	See dosing regimen

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: General Information
- Overall response in the Gamifant clinical trial (NCT01818492**)** 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 (i.e., no fever, no splenomegaly, neutrophils > $1x10^9$/L, platelets > $100x10^9$/L, ferritin < 2,000 µg/L, fibrinogen > 1.50 g/L, D-dimer < 500 ug/L, normal CNS symptoms, no worsening of sCD25 > 2-fold baseline).
  - 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.
- Gamifant is currently not indicated for the treatment of secondary HLH. Secondary HLH generally presents in adults and is triggered by autoimmune disease, infections, or cancer. Treatment for secondary HLH is focused on the triggering condition.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Primary HLH	Initial: 1 mg/kg IV twice per week (every three to four days) Subsequent doses may be increased based on clinical and laboratory criteria	10 mg/kg/dose

VI. Product Availability
Single-dose vial: 10 mg/2 mL, 50 mg/10 mL

VII. References
1. Gamifant Prescribing Information. Geneva, Switzerland: Novimmune; November 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761107s000lbl.pdf. Accessed September 21, 2021.
2. Henter JI, Samuelsson-Horne AC, Arico M, et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood 2002; 100 (7): 2367-72.
3. Chesshyre E, Ramanan AV, Roderick MR. Hemophagocytic Lymphohistiocytosis and Infections: An update. The Pediatric Infectious Disease Journal March 2019; 38(3): e54-e56.
4. Bergsten E, Horne AC, Arico M, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. Blood 2017; 130 (25): 2728-38.
5. Locatelli F, Jordan MB, Allen C, et al. Emapalumab in Children with Primary Hemophagocytic Lymphohistiocytosis. N Engl J Med. 2020 May 7;382(19):1811-1822. doi: 10.1056/NEJMoa1911326. PMID: 32374962.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	12.11.18	02.19
1Q 2020 annual review: no significant changes; references reviewed and updated.	10.29.19	02.20

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2021 annual review: added criteria for diagnosis confirmation per clinical trial inclusion criteria and competitor market analysis; references reviewed and updated.	11.17.20	02.21
1Q 2022 annual review: no significant changes; references reviewed and updated.	09.21.21	02.22

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.