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Last P&T Approval/Version: 07/31/2024
Next Review Due By: 07/2025
Policy Number: C15970-A

Gamifant (emapalumab-lzsg)

PRODUCTS AFFECTED

Gamifant (emapalumab-lzsg)

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Primary hemophagocytic lymphohistiocytosis (HLH)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. PRIMARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH):
1. Documented diagnosis of primary hemophagocytic lymphohistiocytosis (HLH)
   AND

2. Documentation diagnosis was confirmed by ONE of the following [DOCUMENTATION REQUIRED]:
   a. Genetic testing showing a gene mutation known to cause HLH (e.g., PRF1, UNC13D, STX11, etc.)
   OR
   b. Family history consistent with primary HLH with 5 out of the following 8 criteria needing to be fulfilled:
      i. Fever (temperature > 38.5 C for > 7 days)
      ii. Splenomegaly
      iii. Cytopenias affecting 2 of 3 lineages in the peripheral blood: hemoglobin < 9 g/dL platelets <100 $x10^9$/L, neutrophils <1 x 10^9/L
      iv. Hypertriglyceridemia (fasting triglycerides >3 mmol/L or ≥265 mg/dL) and/or hypofibrinogenemia (≤1.5 g/L)
      v. Hemophagocytosis in bone marrow, spleen, or lymph nodes with no evidence of malignancy
      vi. Low or absent natural killer (NK)-cell activity
      vii. Ferritin ≥500 mcg/L
      viii. Soluble CD25 (interleukin [IL]-2 receptor) > 2400 U/mL

   AND
3. Prescriber attests that malignancy, viral infection and rheumatic disorders have been ruled out as a potential primary cause of HLH
   AND
4. Prescriber attests to evidence of currently (within last 3 months) active disease
   AND
5. Documentation member has refractory, recurrent, or progressive disease, or serious side effects with HLH-94 protocol (See Appendix for details) as evidenced by ONE of the following: Having not responded or not achieved a satisfactory response, Having not maintained a satisfactory response to conventional HLH therapy (e.g., dexamethasone, etoposide, cyclosporine A, anti- thymocyte globulin, etc.), OR Serious side effects to conventional HLH treatments
   AND
6. Documentation member is eligible for stem cell transplant and has NOT received hematopoietic stem cell transplant (HSCT)
   AND
7. Prescriber attests Gamifant (emapalumab) is being used prior to HSCT (for induction or maintenance) and will be discontinued when initiating conditioning for stem cell transplant
   AND
8. Documentation of member's baseline disease specific markers including (but not limited to): 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 or other cytokine markers
   AND
9. Prescriber attests member does not have active, untreated, infections caused by specific pathogens favored by IFNγ neutralization (e.g., mycobacteria, herpes zoster, Histoplasma Capsulatum)
   AND
10. Documentation of treatment plan with Gamifant administered concomitantly with dexamethasone
    MOLINA REVIEWER NOTE: Claims may be reviewed for concomitant use of dexamethasone.
    AND
11. Prescriber attests that member will be administered prophylactic treatment against herpes zoster, Pneumocystis jirovecii and fungal infections prior to treatment initiation per the FDA label
    AND
12. (a) Prescriber attests member has had a negative TB screening* OR TB test (if indicated)** result within the last 12 months for initial and continuation of therapy requests
    *MOLINA REVIEWER NOTE: TB SCREENING assesses patient for future or ongoing TB exposure or risk and includes reviewing if they have been exposed to tuberculosis, if they have resided or traveled to areas of endemic tuberculosis, if patient resides or works in a congregate setting (e.g., correctional

facilities, long-term care facilities, homeless shelters), etc.
** MOLINA REVIEWER NOTE: TB SKIN TEST (TST, PPD) AND TB BLOOD TEST (QuantiFERON TB Gold, T-Spot) are not required or recommended in those without risk factors for tuberculosis
OR
(b) For members who have a positive test for latent TB, provider documents member has completed a treatment course (a negative chest x-ray is also required every 12 months) OR that member has been cleared by an infectious disease specialist to begin treatment

CONTINUATION OF THERAPY:

A. PRIMARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH):

1. Documentation member has NOT received hematopoietic stem cell transplant (HSCT) AND continues to require therapy for treatment of HLH
   AND
2. Documentation of improvement in disease-specific markers (may not be a complete list): fever, splenomegaly, central nervous system symptoms, complete blood count, fibrinogen and/or D- dimer, Serum ferritin, lymphocyte and cytokine markers (e.g., soluble IL-2 receptor alpha [sCD25], soluble hemoglobin- haptoglobin scavenger receptor [sCD163]) OR any additional markers that were especially high at diagnosis (e.g., NK cell function, viral titers).
   AND
3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity (i.e., serious infections, severe infusion reactions, etc.)
   AND
4. Documentation of an updated treatment plan addressing ONE of the following: Anticipated hematopoietic stem cell transplant (HSCT), OR if member's treatment plan does not include a HSCT, clinical rationale explaining why HSCT is not appropriate for member at this time.
   AND
5. (a) Prescriber attests member has had a negative TB screening* or TB test (if indicated)** result within the last 12 months for initial and continuation of therapy requests
   *MOLINA REVIEWER NOTE: TB SCREENING assesses patient for future or ongoing TB exposure or risk and includes reviewing if they have been exposed to tuberculosis, if they have resided or traveled to areas of endemic tuberculosis, if patient resides or works in a congregate setting (e.g., correctional facilities, long-term care facilities, homeless shelters), etc.
   ** MOLINA REVIEWER NOTE: TB SKIN TEST (TST, PPD) AND TB BLOOD TEST (QuantiFERON TB Gold, T-Spot) are not required or recommended in those without risk factors for tuberculosis
   OR
   (b) For members who have a positive test for latent TB, provider documents member has completed a treatment course (a negative chest x-ray is also required every 12 months) OR that member has been cleared by an infectious disease specialist to begin treatment

DURATION OF APPROVAL:

Initial authorization: 6 months or up to the HSCT date, whichever is sooner, Continuation of Therapy: 12 months or up to the HSCT date, whichever is sooner

PRESCRIBER REQUIREMENTS:

Prescribed by, or in consultation with, a board-certified geneticist, pediatric metabolic specialist, hematologist, or physician experienced in the management of hemophagocytic lymphohistiocytosis (HLH). [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

No restriction

QUANTITY:

Max of 10 mg/kg/dose IV twice per week

NOTE: Approval quantity should consider titration needs. Refer to dose titration in the product label.

PLACE OF ADMINISTRATION:
The recommendation is that infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-hospital facility-based location.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intravenous infusion

DRUG CLASS:
Monoclonal Antibodies

FDA-APPROVED USES:
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

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
HLH-94 protocol
HLH-94 protocol consists of a series of weekly treatments with dexamethasone and etoposide (VP-16). Intrathecal methotrexate and hydrocortisone are given to those with central nervous system disease. After induction, patients who are recovering are weaned off therapy, while those who are not improving are continued on therapy as a bridge to allogeneic hematopoietic cell transplantation (HCT). HCT will be required in those with an HLH gene mutation, central nervous system disease, or disease relapse.

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Primary HLH is a primarily pediatric, ultra-rare, rapidly progressive, hyperinflammatory syndrome caused by massive hyperproduction of interferon gamma (IFNy) that may lead to organ failure and death if not appropriately treated. Diagnosis of HLH is challenging due to the variability of symptomatic presentation of the disease. Prior to Gamifant, no therapies were FDA-approved for the treatment of primary HLH. Steroids and chemotherapy are typically used off-label prior to hematopoietic stem-cell transplantation (HSCT). Previously believed to be underdiagnosed, more recent estimates suggest that HLH affects 1 in 100,000 persons younger than 18 years. The manufacturer has indicated that fewer than 100 cases of HLH are diagnosed in the United States each year.
Efficacy:
The efficacy of Gamifant was evaluated in a multicenter, open-label, single-arm trial in 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.
Inclusion criteria: Primary HLH based on a molecular diagnosis or family history consistent with primary HLH or 5 out of the 8 criteria fulfilled: Fever, Splenomegaly, Cytopenias affecting 2 of 3 lineages in the peripheral blood: hemoglobin < 9, platelets <100 x 109/L, neutrophils <1 x 109/L, Hypertriglyceridemia (fasting triglycerides >3 mmol/L or ≥265 mg/dL) and/or hypofibrinogenemia (≤1.5 g/L), Hemophagocytosis

in bone marrow, spleen, or lymph nodes with no evidence of malignancy, Low or absent NK-cell activity, Ferritin ≥ 500 mcg/L, Soluble CD25 ≥ 2400 U/mL., Evidence of active disease as assessed by treating physician, One of the following criteria as assessed by the treating physician: Having not responded or not achieved a satisfactory response, Having not maintained a satisfactory response to conventional HLH therapy, and Intolerance to conventional HLH treatments. Patients with active infections caused by specific pathogens favored by IFNγ neutralization (e.g., mycobacteria and Histoplasma Capsulatum) were excluded from the trial.

Patients were started on an initial starting dose of Gamifant of 1 mg/kg every 3 days, with subsequent doses increased to a maximum of 10 mg/kg based on clinical response and laboratory parameters. Most patients (44%) remained at 1 mg/kg, but 30% increased to 3-4 mg/kg and 26% increased to 6- 10 mg/kg. All patients were treated with dexamethasone as background HLH treatment with doses between 5 to 10 mg/m2/day and were allowed continued therapy with cyclosporine, methotrexate, and intrathecal glucocorticoids if these treatments were already administered at baseline. Evaluation of efficacy was based upon 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 based on evaluation of: 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, platelets, ferritin, fibrinogen, D-dimer, 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. The median treatment duration in the clinical trial was 59 days with a range of 4 to 245 days.

Safety:

Commonly reported adverse reactions (≥10%) from the clinical trial included: infection (56%), hypertension (41%), infusion-related reactions (27%), pyrexia (24%), hypokalemia (15%), constipation (15%), rash (12%), abdominal pain (12%), CMV infection (12%), diarrhea (12%), lymphocytosis (12%), cough (12%), irritability (12%), tachycardia (12%), and tachypnea (12%). Additional selected adverse reactions included vomiting, acute kidney injury, asthenia, bradycardia, dyspnea, gastrointestinal hemorrhage, epistaxis, and peripheral edema.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Gamifant (emapalumab-lzsg) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Contraindications to Gamifant include: do not administer live or live attenuated vaccines to patients receiving Gamifant and for at least 4 weeks after the last dose of Gamifant, do not administer to patients with untreated infections caused by mycobacteria, Herpes Zoster virus, and Histoplasma Capsulatum.

OTHER SPECIAL CONSIDERATIONS:

Immunizations: Do not administer live or live attenuated vaccines to patients receiving emapalumab and for at least 4 weeks following the last emapalumab dose (safety of immunization with live vaccines during or following emapalumab has not been studied)

Hypersensitivity reactions, usually a delayed reaction, have been reported following exposure to pharmaceutical products containing polysorbate 80 in certain individuals. Thrombocytopenia, ascites, pulmonary deterioration, and renal and hepatic failure have been reported in premature neonates after receiving parenteral products containing polysorbate 80.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
J9210	Injection, emapalumab-lzsg, 1mg

AVAILABLE DOSAGE FORMS:
Gamifant SOLN 10MG/2ML single-dose vial
Gamifant SOLN 50MG/10ML single-dose vial
Gamifant SOLN 100MG/20ML single-dose vial

REFERENCES

1. Gamifant (emapalumab-lzsg) [prescribing information]. Waltham, MA; Sobi Inc; July 2024.
2. Alade SL, Brown RE, Paquet A Jr. Polysorbate 80 and E-Ferol toxicity. Pediatrics. 1986;77(4):593-597.
3. Centers for Disease Control and Prevention (CDC). Unusual syndrome with fatalities among premature infants: association with a new intravenous vitamin E product. MMWR Morb Mortal Wkly Rep. 1984;33(14):198-199.
4. Isaksson M, Jansson L. Contact allergy to Tween 80 in an inhalation suspension. Contact Dermatitis. 2002;47(5):312-313.
5. Lucente P, Iorizzo M, Pazzaglia M. Contact sensitivity to Tween 80 in a child. Contact Dermatitis. 2000;43(3):172.
6. Shelley WB, Talanin N, Shelley ED. Polysorbate 80 hypersensitivity. Lancet. 1995;345(8960):1312-1313.
7. Henter JI, Samuelsson-Horne A, Aricò M, et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood 2002; 100:2367.
8. Trottestam H, Horne A, Aricò M, et al. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. Blood 2011; 118:4577.
9. Bergsten E, Horne A, Aricó M, et al. Confirmed efficacy of etoposide and dexamethasone in HLH Treatment: long-term results of the cooperative HLH-2004 study. Blood 2017; 130:2728.
10. Henter JI, Horne A, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48:124-31.

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy References	Q3 2024
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Prescriber Requirements Place of Administration Appendix Contraindications/Exclusions/Discontinuation Other Special Considerations Available Dosage Forms References	Q3 2023
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Prescriber Requirements Quantity Contraindications/Exclusions/Discontinuation References	Q3 2022
Q2 2022 Established tracking in new format	Historical changes on file