emapalumab-lzsg (Gamifant™)

Policy # 00678
Original Effective Date: 07/18/2019
Current Effective Date: 08/10/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider emapalumab-lzsg (Gamifant™)‡ for the treatment of primary hemophagocytic lymphohistiocytosis (HLH) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of emapalumab-lzsg (Gamifant) for the treatment of primary hemophagocytic lymphohistiocytosis (HLH) will be considered when the following criteria are met:

- Initial
    - Patient has a diagnosis of primary hemophagocytic lymphohistiocytosis (HLH) determined by at least ONE of the following:
        - Documentation of genetic testing demonstrating homozygosity or compound heterozygosity for verified HLH-associated mutations (e.g., *PRF1*, *UNC13D*, *STX11*, *STXBP2*, *Rab27A*, *SH2D1A*, *BIRC4*, *LYST*, *ITK*, *SLC7A7*, *XMEN*, *HPS*); OR
        - Prior to treatment, the patient meets at least FIVE of the following diagnostic criteria:
            - Fever ≥38.5°C (101.3°F); OR
            - Splenomegaly; OR
            - Cytopenias defined as at least TWO of the following:
                - Hemoglobin <9 g/dL (or <10 g/dL in infants less than 4 weeks of age); OR
                - Platelets <100 $x10^9$/L; OR
                - Neutrophils <$1x10^9$/L; OR

- ❖ Fasting triglycerides ≥265 mg/dL OR fibrinogen ≤1.5 g/L; OR
- ❖ Hemophagocytosis in bone marrow, spleen, or lymph nodes; OR
- ❖ Low or absent natural killer cell activity (according to local laboratory reference); OR
- ❖ Ferritin ≥500 mcg/L; OR
- ❖ Soluble CD25 (i.e., soluble interleukin-2 receptor) ≥2,400 Units/mL; AND

- Patient has tried at least one conventional therapy (e.g., etoposide, cyclosporine A, or anti-thymocyte globulin); AND
- According to the prescriber, patient has experienced at least ONE of the following:
  - Refractory, recurrent, or progressive disease during conventional therapy (e.g., etoposide, cyclosporine A, or anti-thymocyte globulin); OR
  - Intolerance to conventional therapy (e.g., etoposide, cyclosporine A, or anti-thymocyte globulin); AND
- Patient has NOT received a hematopoietic cell transplant (HCT); AND
  *(Note: This specific patient criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient does NOT have secondary HLH (e.g., HLH associated with rheumatic or neoplastic disease); AND
- Gamifant will be administered with dexamethasone; AND
- Patient does NOT have an active infection with a pathogen that is favored by interferon gamma (IFNγ) neutralization (e.g. mycobacteria, Herpes Zoster, *Histoplasma capsulatum*); AND
- Patient will receive prophylaxis for Herpes Zoster, *Pneumocystis jirovecii*, fungal infections, and tuberculosis (if PPD positive); AND
- Dose will not exceed 10 mg/kg administered twice per week.

- Continuation
  - Patient has received an initial authorization for Gamifant; AND
  - Patient has had a beneficial response to treatment based on documented improvement in 3 or more signs of HLH abnormalities; AND
    *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Patient is awaiting HCT or is not a candidate for HCT; AND

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*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

- Dose will not exceed 10 mg/kg administered twice per week.

When Services Are Considered Not Medically Necessary

The use of emapalumab-lzsg (Gamifant) when the patient has received a hematopoietic cell transplant (HCT) or has not experienced a beneficial response to Gamifant treatment is considered to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of emapalumab-lzsg (Gamifant) when the patient selection criteria are not met (except those noted to be **not medically necessary****) to be **investigational.***

Background/Overview

Gamifant is a monoclonal antibody that binds to and neutralizes interferon gamma (IFNγ), a cytokine that is hypersecreted in hemophagocytic lymphohistiocytosis (HLH). It is indicated for patients with primary HLH that is refractory, recurrent, or progressive after conventional therapy has been tried. It is administered as an intravenous infusion twice per week with an initial dose of 1 mg/kg that can be increased up to 10 mg/kg. Dose increases are based on the healthcare provider's assessment of improvement in clinical condition and additional parameters listed in the drug's package insert. Additionally, systemic dexamethasone and prophylaxis for Herpes Zoster, *Pneumocystis jirovecii*, and fungal infections should be administered concomitantly with Gamifant.

Primary HLH is a primarily pediatric, ultra-rare, rapidly progressive, hyperinflammatory syndrome caused by massive hyperproduction of interferon gamma (IFNγ) that may lead to organ failure and death if not appropriately treated. It is caused by defects in cytotoxic function that lead to over-activation of the immune system. The incidence is estimated at 1.2 cases per million individuals per year. Primary HLH differs from secondary HLH in that it has a clear genetic cause, whereas

secondary HLH is triggered by concomitant infection or medical condition such as Epstein-Barr Virus (EBV) infection, malignancy, or rheumatologic disorders. Prior to Gamifant, no therapies were approved by the Food and Drug Administration (FDA) for the treatment of primary HLH. Steroids and chemotherapy are typically used off-label prior to hematopoietic cell transplantation (HCT).

The HLH-2004 treatment protocol, developed by the Histiocyte Society, is the current standard of care for diagnostic and therapeutic guidelines. According to these guidelines, diagnosis must be established by a molecular genetic diagnosis consistent with HLH or five of eight clinical criteria suggesting HLH. Conventional standard of care to induce symptomatic resolution is etoposide and systemic dexamethasone. Cyclosporine A and anti-thymocyte globulin have also demonstrated efficacy. All patients should receive an initial 8 weeks of induction chemotherapy which is known to prolong survival. In primary HLH, HCT is necessary to cure the patient, so patients should continue standard therapy until HCT can be performed. These guidelines do not mention Gamifant, but the FDA has indicated in the approved label that its place in therapy is in patients who failed or cannot tolerate standard therapy for primary HLH.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Gamifant was approved in 2018 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.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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.

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Enrolled patients had 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, hypertriglyceridemia and/or hypofibrinogenemia, 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. Additionally, patients had to have evidence of active disease as assessed by the treating physician. Included patients also had not responded, not achieved or maintained a satisfactory response, or were intolerant to conventional HLH treatments.

The study treatment duration was up to 8 weeks after which patients could continue treatment in the extension study. All patients received an initial starting dose of Gamifant of 1 mg/kg every 3 days. Subsequent doses could be increased to a maximum of 10 mg/kg based on clinical and laboratory parameters interpreted as unsatisfactory response. Throughout the study, 44% of patients remained at a dose of 1 mg/kg, 30% of patients increased to 3-4 mg/kg, and 26% of patients increased to 6-10 mg/kg. The median time to dose increase was 27 days with 22% of patients requiring a dose increase in the first week of treatment. All patients received dexamethasone as background HLH treatment. Cyclosporine A was continued if administered prior to screening. Patients receiving methotrexate and glucocorticoids administered intrathecally at baseline could continue these treatments.

The efficacy of Gamifant 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 using an algorithm that included the following objective clinical and laboratory parameters: fever, splenomegaly, CNS symptoms, complete blood count, fibrinogen and/or D-dimer, ferritin, and soluble CD25 levels. Complete response was defined as normalization of all HLH abnormalities. 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. At the end of treatment, the ORR was found to be 63% (95% CI 0.42, 0.81) with 26% being complete responses, 30% partial responses, and 7.4% HLH improvements.

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References

1. Gamifant [package insert]. Swedish Orphan Biovitrum AB. Stockholm, Sweden. Updated November 2018.
2. Gamifant Prior Authorization Policy. Express Scripts. December 2018
3. Gamifant New Drug Approval. IPD Analytics. November 2018.

Policy History

Original Effective Date: 07/18/2019
Current Effective Date: 08/10/2020
07/03/2019 Medical Policy Committee review
07/18/2019 Medical Policy Implementation Committee approval. New policy.
07/02/2020 Medical Policy Committee review
07/08/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 07/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy

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Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	C9399, J3490, J3590 Code added eff 10/1/19: J9210
ICD-10 Diagnosis	D76.1-D76.3

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.