BlueCross BlueShield of North Carolina

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Corporate Medical Policy

Emapalumab-lzsg (Gamifant™)

File Name:	emapalumab_gamifant
Origination:	3/2019
Last CAP Review:	4/2020
Next CAP Review:	4/2021
Last Review:	4/2020

Description of Procedure or Service

Emapalumab-lzsg (Gamifant) is an interferon gamma (IFNɣ) blocking monoclonal 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.

Hemophagocytic lymphohistiocytosis (HLH) is a rare, severe life-threatening hyperinflammatory disorder involving overproduction of activated immune cells (e.g. T-cells, natural killer cells, B-cells, and macrophages) and cytokines. HLH requires prompt diagnosis and treatment. Symptoms of HLH typically present within the first few months to years of life and can include fever, enlarged spleen or liver, cytopenias, and/or neurological abnormalities. Approximately 25-50% of patients with HLH fail to achieve remission with established regimens that include dexamethasone and etoposide, or methylprednisolone and antithymocyte globulin (ATG). Some of these patients may require salvage or alternative therapeutic approaches. After treatment initiation, recovering patients are tapered off therapy, while those without improvement are continued on therapy as a bridge to hematopoietic stem cell transplantation (HSCT). HSCT is the only curative therapy and is necessary in patients with HLH gene mutation, central nervous system disease, or disease relapse.

Emapalumab-lzsg (Gamifant) was approved by the U.S. Food and Drug Administration (FDA) in November 2018 for the treatment of primary HLH in patients with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy. It works by binding to and neutralizing IFNɣ, which is thought to play a key role in the pathogenesis of HLH due to its hypersecretion.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for emapalumab-lzsg (Gamifant™) for primary hemophagocytic lymphohistiocytosis when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

Emapalumab-lzsg (Gamifant™)

When Emapalumab-lzsg (Gamifant) is covered

Initial Therapy

Emapalumab-lzsg (Gamifant) is considered medically necessary for the treatment of adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH) when the following criteria are met:

1. The patient has a diagnosis of primary HLH based on the following:

   a. Molecular diagnosis by FHL-causative mutations or a family history consistent with primary HLH, and clinical findings associated with HLH; **OR**

   b. Presence of at least five of the following defining symptoms (i.-viii.) at baseline:
      i. Fever (≥38.5ºC)
      ii. Splenomegaly
      iii. Peripheral blood cytopenias defined as at least two of the following:
         a) Hemoglobin < 9 g/dL (for infants age <4 weeks: Hgb < 10 g/dL)
         b) Platelets < 100 x 10^9/L
         c) Neutrophils < 1.0 x 10^9/L
      iv. Hypertriglyceridemia or hypofibrinogenemia defined by one of the following:
         a) Fasting triglycerides ≥ 2.0 mmol/L or >3 SD of the normal value for age
         b) Fibrinogen ≤ 1.5 g/L
      v. Hemophagocytosis in bone marrow, spleen, or lymph nodes
      vi. Low or absent natural killer cell activity
      vii. Ferritin ≥ 500 mcg/L
      viii. Soluble CD25 (soluble IL2Rα) ≥ 2400 U/mL; **AND**

2. The patient has refractory, recurrent, or progressive disease while receiving conventional HLH therapy (i.e., dexamethasone, etoposide, cyclosporine A, and anti-thymocyte globulin) or intolerance to conventional HLH therapy; **AND**

3. The patient has evidence of active disease as assessed by the treating physician; **AND**

4. The patient does not have active infection caused by specific pathogens favored by IFNɣ neutralization (i.e., mycobacteria and *Histoplasma Capsulatum*); **AND**

5. The patient will be receiving dexamethasone concurrently with emapalumab-lzsg; **AND**

6. The patient has not undergone hematopoietic stem cell transplantation (HSCT).

Initial authorization: 6 months

Continuation Therapy

Continuation of treatment with emapalumab-lzsg (Gamifant) beyond 6 months after initiation of therapy, and every 6 months thereafter, is considered medically necessary for the treatment of primary hemophagocytic lymphohistiocytosis (HLH) until one of the following:

- The patient undergoes hematopoietic stem cell transplantation (HSCT), or
- The patient experiences unacceptable toxicity, or
- The patient no longer requires HLH treatment

When Emapalumab-lzsg (Gamifant) is not covered

Emapalumab-lzsg (Gamifant) is considered **investigational** and therefore not covered when the above criteria are not met.

Policy Guidelines

The recommended initial dose for Gamifant is 1 mg/kg administered as an intravenous (IV) infusion over 1 hour two times weekly (every 3 to 4 days). Following the initial dose, subsequent doses may be increased based on the patient's clinical and laboratory data. Gamifant should be administered until hematopoietic stem cell transplantation (HSCT) is performed or until unacceptable toxicity. Gamifant should be discontinued when the patient no longer requires HLH treatment.

Prior to initiation of Gamifant therapy, the patient should be tested for latent tuberculosis (TB) infections using either the purified protein derivative (PPD) or IFNɣ release assay, and evaluated for TB risk factors. Patients at risk for TB, or with a known positive PPD test result or positive IFNɣ release assay, should receive TB prophylaxis. In addition, patients should be monitored for TB, adenovirus, EBV and CMV every two weeks while receiving Gamifant therapy. Prophylaxis for herpes zoster, *Pneumocystis jirovecii*, and fungal infections should also be given prior to Gamifant administration.

Dexamethasone should be administered along with Gamifant. For patients not receiving baseline dexamethasone prior to Gamifant initiation, daily dexamethasone dosing of at least 5 to 10 mg/m^2 should be started the day before beginning Gamifant treatment. Patients already receiving baseline dexamethasone should continue therapy, and at a dose of at least 5 mg/m^2.

According to the manufacturer's safety information for Gamifant, the most common adverse reactions (≥20% incidence) include infections, hypertension, infusion-related reactions, and fever.

Clinical Trial Evidence

The efficacy and safety of emapalumab-lzsg was evaluated in a Phase 2/3, open-label, single-arm, multicenter clinical trial (NCT01818492) of 27 pediatric patients (≤18 years of age at diagnosis) with suspected or confirmed primary HLH with either refractory, recurrent, or progressive disease during use of conventional HLH therapy or who are intolerant to conventional HLH therapy. Patients included in the trial had a diagnosis of primary HLH based on a molecular diagnosis or a family history consistent with primary HLH, or presence of at least five out of eight defining symptoms [i.e. fever, splenomegaly, cytopenias affecting 2/3 lineages in the peripheral blood (Hgb < 9, platelets < 100x10^9/L, neutrophils < 1x10^9/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]. Patients also had evidence of active disease as evaluated by the treating physician, and must have met one of the following scenarios, as also confirmed by the treating physician: having not responded or not achieved a satisfactory response or not maintained a satisfactory response to conventional HLH therapy, or intolerance to conventional HLH treatments. All patients received previous HLH treatment with combinations with the following agents: dexamethasone, etoposide, cyclosporine A, and anti-thymocyte globulin. A median of 3 prior agents were received prior to patient enrollment into the trial. Patients with active infections caused by specific pathogens favored by IFNɣ neutralization (i.e. mycobacteria and *Histoplasma*

capsulatum) were excluded from the study, and enrolled patients received prophylaxis for herpes zoster, *Pneumocystis jirovecii*, and fungal infections.

A total of 27 patients received emapalumab treatment in the trial; 20 patients (74%) completed the study and 7 patients (26%) were withdrawn prematurely. Twenty-two patients (81%) were enrolled in the open-label extension study that monitored patients for up to one year following HSCT or following the last emapalumab infusion (NCT02069899). All patients received an initial dose of emapalumab 1 mg/kg every 3 days, and subsequent doses could be increased to a maximum of 10 mg/kg based on patient clinical and laboratory parameters interpreted as unsatisfactory response. All patients received dexamethasone as background HLH treatment with dosage range from 5 to 10 mg/m^2/day. Treatment duration was up to 8 weeks after which patients could then continue treatment in the extension study.

The primary endpoint was overall response rate (ORR) at treatment end, defined as achievement of either a complete or partial response or HLH improvement. The ORR was 63% (17/27 patients; 95% CI, 0.42 to 0.81; p=0.013) with observation of complete response in 7/27 patients (26%), partial response in 8/27 patients (30%), and HLH improvement in 2/27 patients (7.4%). Other endpoints included time to response, durability of response, survival, glucocorticoid tapering, and safety/tolerability. Seventy percent (19/27) of patients proceeded to HSCT.

The following information is derived from FDA prescribing information, as peer reviewed published trial results have not been identified.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: *J9210*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Sobi Inc. Gamifant (emapalumab-lzsg) injection, for intravenous use. Highlights of prescribing information. November 2018. Available at: https://gamifant.com/pdf/Full-Prescribing-Information.pdf. Accessed February 2019.

U.S. Food and Drug Administration. FDA approves first treatment specifically for patients with rare and life-threatening type of immune disease. Available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm626263.htm. Accessed February 2019.

Zhang K, Filipovich AH, Johnson J, et al. Hemophagocytic lymphohistiocytosis, familial. 2006 Mar 22 [Updated 2013 Jan 17]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1444/. Accessed March 2019.

Medical Director review 4/2019

Specialty Matched Consultant Advisory Panel 11/2019

Specialty Matched Consultant Advisory Panel 4/2020

Policy Implementation/Update Information

4/16/19 New policy developed. Gamifant is considered medically necessary for the treatment of adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH). Added HCPCS codes C9399, J3490, and J3590 to Billing/Coding section. References added. Medical Director review 4/2019. (krc)

7/1/19 Added HCPCS code C9050 to Billing/Coding section and deleted code C9399. (krc)

10/1/19 Added HCPCS code J9210 to Billing/Coding section and deleted codes C9050, J3490, and J3590 effective 10/1/19. (krc)

12/2/19 Specialty Matched Consultant Advisory Panel review 11/20/2019. No change to policy intent. (krc)

6/9/20 Specialty Matched Consultant Advisory Panel review 4/15/2020. No change to policy intent. (krc)