09-J3000-24

Original Effective Date: 04/01/19

Reviewed: 02/13/19

Revised: 10/01/19

Subject: Emapalumab-lzsg (Gamifant) IV

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening hyperinflammatory syndrome of intense immune activation caused by defects in cytotoxic pathways which leads to an increase in cytokines and accumulation of activated macrophages in organs and tissues. Symptoms may include fever, enlarged liver or spleen, cytopenias, neurologic abnormalities, and progression to multiorgan failure. HLH can be inherited (primary) or acquired (secondary). Primary HLH typically develops during the first months or years of life, although it may also develop later in life. Diagnostic criteria for HLH were developed by the Histiocyte Society and consist of either molecular confirmation of HLH or at least 5 of 8 specific clinical features. Treatment includes chemotherapy or immunotherapy until allogeneic hematopoietic stem cell transplant can occur.

Interferon gamma is a proinflammatory cytokine that is secreted in HLH. Emapalumab-lzsg (Gamifant) is a monoclonal antibody that binds to and neutralizes interferon gamma. It is Food and Drug Administration (FDA) approved for the treatment of adult and pediatric (newborn and older) patients with primary HLH with refractory, recurrent or progressive disease, or intolerance with conventional HLH therapy.

Emapalumab was evaluated in a 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. Patients were included if there was evidence of active disease by physician assessment and were 18 years of age or younger at diagnosis of Primary HLH. Patients were included with primary HLH if based on molecular diagnosis, family history consistent with the disease, or five out of 8 of the following were fulfilled: fever, splenomegaly, cytopenia affecting 2 of 3 lineages in the peripheral blood (hemoglobin < 9 g/dL, platelets < 100 x 10^9/L, neutrophils < 1 x 10^9/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 were included if they did not respond or maintain a response to conventional HLH treatment, or had intolerance to conventional treatment. Prior HLH treatments included combinations of

the following: dexamethasone, etoposide, cyclosporine A, and anti-thymocyte globulin. All patients received dexamethasone in the trial and could continue cyclosporine A or intrathecal methotrexate or glucocorticoids if receiving prior to treatment. Patients were excluded if malignancy was present or if there was secondary HLH due to rheumatic or malignant disease. Patients were excluded for active infections caused by pathogens favored by interferon gamma neutralization (e.g., mycobacteria and Histoplasma capsulatum) but were allowed to enroll for other active infections. All patients received prophylaxis for Herpes Zoster, Pneumocystis jirovecii and fungal infections.

There were 27 patients enrolled and the median patient age was 1 year (0.2 – 13). Eighty-two percent of patients had a genetic mutation known to cause primary HLH. Twenty patients completed the study at 8 weeks and 22 enrolled in the 1 year extension study. All patients received an initial dose of 1 mg/kg every 3 days. There were 30% of patients who increased the dose to 3-4 mg/kg and 26% who increased to 6-10 mg/kg. Efficacy was assessed by overall response rate (ORR) at the end of treatment using clinical and lab parameters and was defined as achievement of either a complete or partial response or HLH improvement. Complete response was defined as normalization of all HLH abnormalities (no fever, no splenomegaly, neutrophils > 1 x 10^9/L, platelets >100 x 10^9/L, ferritin < 2,000 mcg/L, fibrinogen > 1.5 g/L, D-dimer <500 mcg/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. The ORR was achieved by 17/27 patients (63%, p=0.013) with 7 (26%), 8 (30%), and 2 (7.4%) patients achieving a complete response, partial response or HLH improvement, respectively. Seventy percent (19/27) of patients proceeded to HSCT. The most common adverse reactions (≥ 20%) included infections, hypertension, infusion-related reactions, and pyrexia. The most common serious adverse reactions (≥ 3%) included infections, gastrointestinal hemorrhage, and multiple organ dysfunction. Fatal adverse reaction occurred in two patients and included septic shock and gastrointestinal hemorrhage. Disseminated histoplasmosis led to drug discontinuation in one patient.

POSITION STATEMENT:

Initiation of emapalumab-lzsg (Gamifant) **meets the definition of medical necessity** for the treatment of the following indications when all of the specific criteria are met:

1. Primary hemophagocytic lymphohistiocytosis (HLH)

A. **ONE** of the following - documentation must be submitted:

i. Presence of a primary HLH genetic mutation (e.g., FHL2-PRF1, FHL3-UNC13D, FLH4-STX11, FLH5-STXBP2 (UNC18B), RAB27A, LYST, SH2D1A, BIRC4, AP3B1)

ii. At least 5 of the following 8 clinical signs of primary HLH:

1. Fever
2. Splenomegaly
3. Cytopenia affecting at least 2 of 3 lineages in the peripheral blood (hemoglobin < 9 g/dL, platelets < 100 x 10^9/L, neutrophils < 1 x 10^9/L)
4. Hypertriglyceridemia (fasting triglycerides ≥ 3 mmol/L or ≥ 265 mg/dL) and/or hypofibrinogenemia (≤ 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

B. Member has evidence of active disease

C. Member is less than or equal to 18 years of age at diagnosis of Primary HLH

D. Member has an inadequate response, intolerance, or contraindication to conventional HLH therapy (e.g., combined use of dexamethasone, etoposide, and cyclosporine A)

E. Member does not have secondary HLH (e.g., HLH associated with rheumatic or neoplastic disease)

F. Member does not have an active infection with Herpes Zoster, Mycobacteria, Histoplasma Capsulatum, Shigella, Salmonella, Campylobacter, or Leishmania

G. Member will receive prophylaxis for Herpes Zoster, Pneumocystis jirovecii, fungal infections, and tuberculosis (if PPD positive)

H. Member will receive dexamethasone in combination with emapalumab-lzsg

I. Emapalumab-lzsg will be discontinued when the member receives a hematopoietic stem cell transplant

J. The dose does not exceed the following:

i. 1 mg/kg intravenously every 3 to 4 days initially

ii. 3 mg/kg every 3 to 4 days beginning on day 3 if there is unsatisfactory improvement in clinical condition

iii. 6 mg/kg every 3 to 4 days beginning on day 6 if there is unsatisfactory improvement in clinical condition

iv. 10 mg/kg every 3 to 4 days beginning on day 9 if there is unsatisfactory improvement in clinical condition

v. After stabilization of the member's clinical condition, the dose will be decreased to the minimum effective dose

Approval duration: 8 weeks

Continuation of emapalumab-lzsg (Gamifant) **meets the definition of medical necessity** for the treatment of primary HLH when **ALL** of the following criteria are met:

1. An authorization or reauthorization for emapalumab-lzsg (Gamifant) has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of primary HLH, **OR** the member has previously met **ALL** indication-specific criteria.
2. Member has a beneficial response to treatment (e.g., improvement in at least 3 or more signs of HLH abnormalities) – documentation must be submitted
3. Member does not have secondary HLH (e.g., HLH associated with rheumatic or neoplastic disease)
4. Member does not have an active infection with Herpes Zoster, Mycobacteria, Histoplasma Capsulatum, Shigella, Salmonella, Campylobacter, or Leishmania
5. Member will receive prophylaxis for Herpes Zoster, Pneumocystis jirovecii, fungal infections, and tuberculosis (if PPD positive)
6. Member will receive dexamethasone in combination with emapalumab-lzsg
7. Emapalumab-lzsg will be discontinued when the member receives a hematopoietic stem cell transplant

8. The dose does not exceed 10 mg/kg every 3 to 4 days – the dose will be titrated to the minimum dose effective to stabilize the member's clinical condition

Approval duration: 6 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent or progressive disease, or intolerance with conventional HLH therapy: 1 mg/kg as an intravenous infusion over 1 hour twice per week (every 3 to 4 days). Doses subsequent to the initial dose may be increased based on clinical and lab data. . Discontinue when hematopoietic stem cell transplantation (HSCT) is performed, unacceptable toxicity, or when a patient no longer requires therapy for treatment of HLH.
- Conduct testing for latent tuberculosis infection prior to therapy. Administer tuberculosis prophylaxis to patients at risk or who test positive. Monitor for tuberculosis, adenovirus, EBV, and CMV every 2 weeks and as clinically indicated.
- Administer prophylaxis for Herpes Zoster, Pneuomocystis jirovecii, and for fungal infections prior to administration.
- Administer dexamethasone at a daily dose of at least 5 mg/m^2 to 10 mg/m^2 concomitantly; If dexamethasone was already being taken, the dose may be continued if at least 5 mg/m^2

Dose Adjustments

- See prescribing information for dose titration for unsatisfactory improvement in clinical condition (fever, platelet, neutrophil, ferritin, splenomegaly, coagulopathy, fibrinogen). Dose is adjusted from day 1 (1 mg/kg), day 3 (3 mg/kg), day 6 (6 mg/kg), and day 9 (up to 10 mg/kg) based on clinical condition. After the patient's clinical condition is stabilized, decrease the dose to the previous level to maintain clinical response.

Drug Availability

- 10 mg/2 mL (5 mg/mL)
- 50 mg/10 mL (5 mg/mL)

PRECAUTIONS:

Contraindications

- None

Precautions/Warnings

- Infections – may increase the risk of fatal and serious infections to include specific pathogens favored by interferon gamma neutralization, including mycobacteria, Herpes Zoster virus, and Histoplasma Capsulatum. Do not administer in patients with infections caused by these pathogens until appropriate treatment has been initiated.
- Live Vaccines: Do not administer live or live attenuated vaccines to patients receiving emapalumab and for at least 4 weeks following the last dose.

- Infusion reactions: Drug eruption, pyrexia, rash, erythema, and hyperhidrosis were reported in up to 27% of patients. Monitor for infusion related reaction and interrupt infusion to initiate appropriate medical care.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J9210	Injection, emapalumab-lzsg, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

D76.1	Hemophagocytic lymphohistiocytosis

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage:

- No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

none

RELATED GUIDELINES:

none

OTHER:

none

REFERENCES:

1. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2019 [cited 2019 Jan 28]. Available from: http://www.clinicalpharmacology.com/.
2. ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/record/NCT02069899. Accessed 1/30/19.

3. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2019 Jan 28]. Available from: http://www.thomsonhc.com/.
4. National Institutes of Health. Genetic and Rare Diseases Information Center Website. https://rarediseases.info.nih.gov/diseases/6589/hemophagocytic-lymphohistiocytosis Accessed 1/30/2019.
5. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2019 [2019 Jan 28]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
6. Gamifant (emapalumab-lzsg)[package insert]. Sobi, Inc. Waltham, MA. November 2018.
7. Weitzman S. Approach to Hemophagocytic syndromes. Hematology. 2011: 178-183.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the BCBSF Pharmacy Policy Committee on 02/13/19.

GUIDELINE UPDATE INFORMATION:

04/01/19	New Medical Coverage Guideline.
07/01/19	Revision: Added HCPCS code C9050.
10/01/19	Revision: Added HCPCS J9210 and removed C9050 and J3590.