Medical Benefit Injectable Clinical Criteria

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**Next Review Date** ....................................... 11/1/2021
**Coverage Policy Number** ............................... M0012

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**Emapalumab-lzsg**

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**Related Coverage Resources**
- Medication Administration Site of Care - 1605
- Unassigned Drug or Biologic Code Medical
  Precertification - 1701

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**INSTRUCTIONS FOR USE**
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

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**Medical Necessity Criteria**

Emapalumab-lzsg (Gamifant™) is considered medically necessary when ALL of the following criteria are met:

- Treatment of primary hemophagocytic lymphohistiocytosis (HLH) and ONE of the following:
  - Confirmed biallelic pathogenic or likely pathogenic variants in any of the following genes: PRF1, UNC13D, STX11, STXBP2, or RAB27A List criteria 2
  - Confirmed pathogenic or likely pathogenic variant in either XIAP or SH2D1A
  - Documentation of at least FIVE of the following diagnostic criteria from the American Histiocyte Society:
    - Persistent fever
    - Splenomegaly
    - Cytopenia involving at least 2 cell lines (hemoglobin less than 9 g/dL, absolute neutrophil count less than 100 µL, platelets less than 100,000/µL)
    - Hypertriglyceridemia (fasting triglycerides greater than 2.0 mmol/L or greater than 3 standard deviations more than normal value for age) or hypofibrinogenemia (fibrinogen less than 1.5 g/L or greater than 3 standard deviations less than normal value for age)
    - Hemophagocytosis in bone marrow, spleen, or lymph nodes with no evidence of malignancy
    - Low or absent natural killer (NK)-cell activity
    - Serum ferritin greater than 500 mcg/L
- Elevated soluble interleukin-2 (CD25) levels (greater than 2400 U/mL or very high for age)
- Evidence of active disease (for example, fever, splenomegaly, central nervous system symptoms, cytopenia, elevated fibrinogen and/or D-dimer, elevated ferritin, and elevated soluble CD25 [also referred to as soluble interleukin-2 receptor] levels)
- Refractory, recurrent, or progressive disease, or intolerance to conventional HLH therapy (for example, corticosteroids, cyclosporine, etoposide, methotrexate)

Initial authorization is up to 3 months.

Emapalumab-lzsg is considered medically necessary for continued use when the following are met:
- Documentation of clinical response (improvement in any of the clinical or laboratory parameters used to demonstrate evidence of active disease on initial authorization), but also evidence of residual active disease
- Dose titration has occurred to the minimum dose and frequency to achieve sustained clinical effect as recommended by FDA labeling of Gamifant (emapalumab-lzsg)
- Individual has not received a successful hematopoietic stem cell transplant

Reauthorization is for 3 months.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Emapalumab-lzsg is considered experimental, investigational or unproven for ANY other use.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

**FDA Approved Indications**

**FDA Approved Indication**
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.

**Recommended Dosing**

**FDA Recommended Dosing**
The recommended starting dose of Gamifant is 1 mg/kg given as an intravenous infusion over 1 hour twice per week (every three to four days). Doses subsequent to the initial dose may be increased based on clinical and laboratory criteria.

Administer Gamifant until hematopoietic stem cell transplantation (HSCT) is performed or unacceptable toxicity. Discontinue Gamifant when a patient no longer requires therapy for the treatment of HLH.

**Drug Availability**
Supplied as 10 mg/2 mL (5 mg/mL) and as 50 mg/10 mL (5 mg/mL) in single-dose vials.

**Background**

**Professional Societies/Organizations**
The Pediatric Blood Cancer journal published guidelines for the diagnosis and treatment of HLH in 2007. Diagnosis is based on a molecular diagnosis (for example, presence of specific genetic mutations) or clinical symptoms and a variety of specialized laboratory tests. (Henter, 2007) Patients without a molecular diagnosis
must have 5 of the following 8 criteria to receive a clinical diagnosis. (Henter, 2007) Table 1 lists the guideline-recommended criteria for diagnosis.

**Table 1. Guideline-Recommended Criteria for Clinical Diagnosis**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Threshold for Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytopenias</td>
<td></td>
</tr>
<tr>
<td>• Hemoglobin</td>
<td></td>
</tr>
<tr>
<td>o Infants &lt; 4 wk: &lt; 10 g/dL</td>
<td></td>
</tr>
<tr>
<td>o All others: &lt; 9 g/dL</td>
<td></td>
</tr>
<tr>
<td>• Neutrophils: &lt; 1,000/mm³</td>
<td></td>
</tr>
<tr>
<td>• Platelets &lt; 100,000/mm³</td>
<td></td>
</tr>
<tr>
<td>Elevated soluble interleukin-2 receptors</td>
<td>CD25 ≥ 2,400 units/mL</td>
</tr>
<tr>
<td>Ferritinemia</td>
<td>Ferritin ≥ 500 ng/mL</td>
</tr>
<tr>
<td>Fever</td>
<td>Any fever</td>
</tr>
<tr>
<td>Hemophagocytosis in bone marrow, lymph nodes, or spleen</td>
<td>Assess per biopsy or bone marrow aspirate</td>
</tr>
<tr>
<td>Hypertriglyceridemia or hypofibrinogenemia</td>
<td></td>
</tr>
<tr>
<td>• Fasting triglyceride ≥ 265 mg/dL</td>
<td></td>
</tr>
<tr>
<td>• Fibrinogen ≤ 150 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Low or absent natural killer cell activity</td>
<td>Assess per local laboratory thresholds</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Any worsening on exam</td>
</tr>
</tbody>
</table>

*Data derived from Henter et al. (Henter, 2007)*

Treatment guidelines and the National Organization for Rare Disorders (NORD) discuss preferred treatment options. (Jordan, 2019; Henter, 2007) Treatment is targeted towards each patient’s predominant symptoms, with the goal of decreasing inflammation, destroying hyperactive immune cells, and preparing patients for hematopoietic stem cell transplantation. (FDA 2018; Jordan, 2019) Options include etoposide or teniposide in combination with steroids or cyclosporine. (Jordan, 2019; Henter, 2007) Dexamethasone is the preferred steroid in CNS disease due to improved CNS penetration. Intrathecal methotrexate can be used in patients with CNS disease who do not improve with systemic therapy. (Jordan, 2019; Henter, 2007) Antithymocyte globulin is also effective in treating primary HLH. (Henter, 2007) Chemotherapy and steroids do not cure disease. (Jordan, 2019; Henter, 2007) The acute treatment of a disease flare may last up to 8 weeks, after which medications are weaned according to patient response. (Jordan, 2019) Hematopoietic stem cell transplantation is the only curative therapy available. It is recommended in patients with primary HLH, patients who do not respond to acute treatment, and patients with CNS involvement or an untreated hematologic cancer, since transplant can improve overall survival. (FDA 2018; Jordan, 2019; Henter, 2007) Emapalumab’s place in therapy is not discussed in guidelines or in NORD recommendations. (Jordan, 2019; Henter, 2007)

**The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative**

No recommendations are available for emapalumab-lzsg.

**Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)**

There are no CMS National Coverage Determinations for emapalumab-lzsg.

**Off Label Uses**

AHFS Drug Information 2020 Edition does not support any off-label uses of emapalumab-lzsg.

**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.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:
<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C9050</td>
<td>Injection, emapalumab-lzsg, 1 mg (Code deleted 09/30/2019)</td>
</tr>
<tr>
<td>J9210</td>
<td>Injection, emapalumab-lzsg, 1 mg</td>
</tr>
</tbody>
</table>

**References**


