Clinical Policy Title:	emapalumab-lzsg
Policy Number:	RxA.142
Drug(s) Applied:	Gamifant®
Original Policy Date:	02/07/2020
Last Review Date:	03/09/2021
Line of Business Policy Applies to:	All lines of business

Background

Emapalumab-lzsg (Gamifant®) is an interferon gamma (IFNγ) blocking antibody. 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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
emapalumab-lzsg (Gamifant®)	Primary HLH	1 mg/kg IV twice per week (every three to four days)	10 mg/kg/dose, 2 doses per week

Dosage Forms

- Single-dose vial: 10 mg/2 mL, 50 mg/10 mL

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

I. Initial Approval Criteria

A. Primary Hemophagocytic Lymphohistiocytosis (must meet all)**:**

1. Diagnosis of primary HLH [i.e., familial (inherited) HLH];
2. Prescribed by or in consultation with a hematologist, oncologist, immunologist, or transplant specialist;
3. Failure of conventional primary HLH therapy including etoposide, dexamethasone, cyclosporine A ± intrathecal methotrexate unless contraindicated or clinically significant adverse effects are experienced;
4. Documentation of a scheduled bone marrow or hematopoietic stem cell transplantation (HSCT) or identification of a transplant donor is in process;
5. Dose does not exceed 10 mg/kg per dose, two doses per week;
6. Member does not have any active infections caused by to specific pathogens favored by IFNγ neutralization, including mycobacteria, Herpes Zoster virus, and Histoplasma Capsulatum;
7. Documentation of latent tuberculosis (TB) test result (purified protein derivative test or IFNγ release assay) showing negative result or supporting documentation showing member is taking prophylactic TB treatment (e.g. isoniazid) if member is at risk for TB, or known to have a positive test result;

8. Members should have documented concurrent dexamethasone therapy or plan to initiate it.

Approval duration
Commercial: 2 months
Medicaid: 2 months

II. Continued Therapy Approval

A. Primary Hemophagocytic Lymphohistiocytosis (must meet all)**:**

1. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy – including but not limited to improvement in any of the following parameters:
   a. Fever reduction;
   b. Splenomegaly;
   c. Central nervous system symptoms;
   d. Complete blood count;
   e. Fibrinogen and/or D-dimer;
   f. Ferritin;
   g. Soluble CD25 (also referred to as soluble interleukin-2 receptor) levels;
3. If request is for a dose increase, new dose does not exceed 10 mg/kg per dose, two doses per week.

Approval duration
Commercial: 6 months
Medicaid: 6 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
HLH: hemophagocytic lymphohistiocytosis
HSCT: hematopoietic stem cell transplantation

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Maximum Dose
etoposide (Toposar®) (Part of preferred HLH-94 treatment protocol)	Initial therapy for first 8 weeks: 150 mg/m^2 IV twice weekly for 2 weeks and then weekly for an additional 6 weeks. Continuation therapy from week 9 until HSCT or BMT: 150 mg/m^2 every alternating second week in combination with daily oral cyclosporine	150 mg/m^2 per dose

Drug Name	Dosing Regimen	Maximum Dose
dexamethasone (Part of preferred HLH-94 treatment protocol)	Initial therapy: 10 mg/m^2 PO or IV for 2 weeks followed by 5 mg/m^2 for 2 weeks, 2.5 mg/m^2 for 2 weeks, 1.25 mg/m^2 for 1 week, and 1 week of tapering Continuation therapy from week 9 until HSCT or BMT: 10 mg/m^2 for 3 days every second week	See dosing regimen
Cyclosporine A (Part of preferred HLH-94 treatment protocol)	Continuation therapy: Starting at week 9, 6mg/kg daily in divided doses (target trough level 200 mcg/L)	N/A
methotrexate (Part of preferred HLH-94 treatment protocol)	Start only if progressive neurological symptoms or if an abnormal CSF has not improved. Treat intrathecally from week 3 to week 6 weekly at doses: • Age < 1 yr = 6 mg per dose • Age 1-2 yrs = 8 mg per dose • Age 2-3 yrs = 10 mg per dose • Age > 3 yrs = 12 mg per dose	See dosing regimen

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - None reported.

- Boxed Warning(s):
  - None reported.

APPENDIX D: General Information

- Overall response in the Gamifant® clinical trial (NCT01818492) was evaluated using an algorithm that included the following objective clinical and laboratory parameters: 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 > 1x10^9/L, platelets > 100x10^9/L, ferritin < 2,000 µg/L, fibrinogen > 1.50 g/L, D-dimer < 500 ug/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.
- Gamifant® is currently not indicated for the treatment of secondary HLH. Secondary HLH generally presents in adults and is triggered by autoimmune disease, infections, or cancer. Treatment for secondary HLH is focused on the triggering condition.

References

1. Gamifant® Prescribing Information. Geneva, Switzerland: Novimmune; June 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761107s000lbl.pdf. Accessed January 25, 2021.
2. Henter JI, Samuelsson-Horne AC, Arico M, et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood 2002; 100 (7): 2367-72.
3. Chesshyre E, Ramanan AV, Roderick MR. Hemophagocytic Lymphohistiocytosis and Infections: An update. The Pediatric Infectious Disease Journal March 2019; 38(3): e54-e56.
4. Bergsten E, Horne AC, Arico M, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. Blood 2017; 130 (25): 2728-38.
5. La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood. 2019 Jun 6;133(23):2465-2477. doi: 10.1182/blood.2018894618. Epub 2019 Apr 16. PMID: 30992265. Accessed January 25, 2021.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy was established	01/2020	02/07/2020
Policy was reviewed: 1. Added tuberculosis testing criteria to initial approval criteria. 2. References updated.	04/2020	05/21/2020
Policy was reviewed. 1. Policy title table was updated. 2. Initial approval criteria I.A.3 was updated to include intrathecal methotrexate in therapy. 3. Approval duration section was updated for initial and continued therapy approval. 4. Appendix B standard verbiage was updated. Table was also updated to clarify that the products in this section are all part of a preferred regimen. Methotrexate was added to table as well as part of HLH-94 treatment protocol. 5. Continued therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance...". 6. Reference reviewed and updated.	01/25/2021	03/09/2021