POLICY: Gamifant® (emapalumab-lzsg for intravenous injection – Sobi)

DATE REVIEWED: 12/18/2019

OVERVIEW

Gamifant is a fully human monoclonal antibody against interferon gamma (IFN-γ).[1] It is indicated for the treatment of adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH) [also referred to as familial HLH] with refractory, recurrent, or progressive disease or intolerance with conventional HLH therapy. Per product labeling, Gamifant should be administered concomitantly with systemic dexamethasone and with prophylaxis for Herpes Zoster, *Pneumocystis jirovecii*, and fungal infections. The initial starting dose of Gamifant is 1 mg/kg twice weekly (once every 3 to 4 days).[1] Dose increases up to a maximum 10 mg/kg twice weekly may be considered for subsequent doses if there is unsatisfactory improvement in clinical condition and laboratory parameters. Refer to the Gamifant prescribing information for recommended dose titration schedule and criteria.

HLH is a syndrome characterized by signs and symptoms of extreme inflammation, caused by defects in cytotoxic function that lead to over-activation of the immune system.[2] The incidence is estimated at 1.2 cases per million individuals per year, but this is likely an underestimate.[3] Cytotoxic function is an important process in immune regulation; by inducing apoptosis in activated immune cells, effector cells (cytotoxic T cells or natural killer [NK] cells) terminate the immune response when appropriate. Deficiencies in cytotoxic function lead to hyper-inflammation as effector cells are unable to silence activated immune cells via apoptosis. Sustained hyper-inflammation leads to multi-organ damage, with the liver being most commonly affected.[2,3] HLH can be classified as primary or secondary. Primary HLH has a clear genetic cause, whereas secondary HLH is triggered by a concomitant infection or medical condition, such as Epstein-Barr Virus (EBV) infection, malignancy, or rheumatologic disorders.

IFN-γ has an important role in immune regulation and in HLH pathophysiology.[4,5] Pro-inflammatory effects of IFN-γ include macrophage activation, upregulation of antigen presentation pathways, and stimulation of cytokines including interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, and others. In healthy individuals, IFN-γ also exerts anti-inflammatory effects by activating cytotoxic T lymphocytes and NK cells, inducing apoptosis and silencing the immune response. In HLH, due to impaired activity of cytotoxic T cells and NK cells, INF-γ is unable to exert anti-inflammatory effects. Thus the pro-inflammatory effects are unbalanced, resulting in immune over-activation. Additionally, IFN-γ is thought to be hyper-secreted as a result of deficient cytotoxic activity.[1]

Guidelines

The HLH-2004 treatment protocol, developed by the Histiocyte Society, is the current standard of care for diagnostic and therapeutic guidelines.[6] To establish a diagnosis of HLH, patients must either have a molecular diagnosis consistent with HLH or must meet five out of eight diagnostic criteria. A backbone of etoposide and systemic dexamethasone is the conventional standard of care to induce symptomatic resolution; cyclosporine A and anti-thymocyte globulin have also demonstrated efficacy. All patients should receive an initial 8 weeks of induction chemotherapy. Patients with secondary HLH may be able to stop chemotherapy (though it should be resumed if reactivation occurs); secondary HLH has a highly variable course and has been reported to sometimes resolve with resolution of the underlying disease.[3,6] By contrast, although chemotherapy prolongs survival in primary HLH, a hematopoietic stem cell transplant (HSCT) is needed for cure. Patients with primary HLH should continue chemotherapy (usually with etoposide, cyclosporine A, and dexamethasone) until HSCT can be performed. Myelotoxicity due to

chemotherapy is a concern, especially since patients with HLH can have severe cytopenias and immunodeficiency at baseline.

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Gamifant. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for 6 months in duration. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Gamifant, approval requires it to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

1. **Hemophagocytic Lymphohistiocytosis, Primary.** Approve Gamifant for 6 months in patients meeting all of the following criteria (A, B, C, and D):
   - **A)** The patient has a diagnosis of hemophagocytic lymphohistiocytosis determined by at least one of the following (i or ii):
     - **i.** The patient has a molecular genetic diagnosis consistent with hemophagocytic lymphohistiocytosis; OR
     - **ii.** Prior to treatment, the patient meets at least FIVE of the following diagnostic criteria at baseline (FIVE of: a, b, c, d, e, f, g, or h):
       - **a)** Fever ≥ 38.5 °C;
       - **b)** Splenomegaly;
       - **c)** Cytopenias defined as at least TWO of the following (1, 2, or 3):
         - **1)** Hemoglobin < 9 g/dL (or < 10 g/dL in infants less than 4 weeks of age);
         - **2)** Platelets < 100 x 10^9/L;
         - **3)** Neutrophils < 1.0 x 10^9/L;
       - **d)** Fasting triglycerides ≥ 265 mg/dL OR fibrinogen ≤ 1.5 g/L;
       - **e)** Hemophagocytosis in bone marrow, spleen, or lymph nodes;
       - **f)** Low or absent natural killer cell activity (according to local laboratory reference);
       - **g)** Ferritin ≥ 500 mcg/L;
       - **h)** Soluble CD25 (i.e., soluble interleukin-2 receptor) ≥ 2,400 U/mL; AND
   - **B)** The patient has tried at least one conventional therapy (e.g., etoposide, cyclosporine A, or anti-thymocyte globulin); AND
   - **C)** According to the prescriber, the patient has experienced at least ONE of the following (i or ii):
     - **i.** Refractory, recurrent, or progressive disease during conventional therapy (e.g., etoposide, cyclosporine A, or anti-thymocyte globulin); OR
     - **ii.** Intolerance to conventional therapy (e.g., etoposide, cyclosporine A, or anti-thymocyte globulin); AND
   - **D)** The medication is prescribed by, or in consultation with, a hematologist, oncologist, immunologist, transplant specialist, or physician who specializes in hemophagocytic lymphohistiocytosis or related disorders.

Dosing.[1] Approve up to a maximum dose of 10 mg/kg by intravenous infusion, not more frequently than twice weekly (once every 3 to 4 days).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Gamifant has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Gamifant® [prescribing information]. Waltham, MA: Sobi, Inc; November 2018.
2. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood*. 2011;118(15):4041-4052.
3. Weitzman S. Approach to hemophagocytic syndromes. *Hematology Am Soc Hematol Edu Program.* 2011;2011:178-183.
4. Avau A, Matthys P. Therapeutic potential of interferon-γ and its antagonists in autoinflammation: lessons from murine models of systemic juvenile idiopathic arthritis and macrophage activation syndrome. *Pharamceuticals.* 2015;8:793-815.
5. Osinska I, Popko K, Demkow U. Perforin: an important player in immune response. *Centr Eur J Immunol*. 2014;39(1):109-115.
6. Henter J, Horne A, Aricó M, et al. HLH-2004: Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48:124-131.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New policy	--	12/19/2018
Annual revision	No changes to criteria	12/18/2019