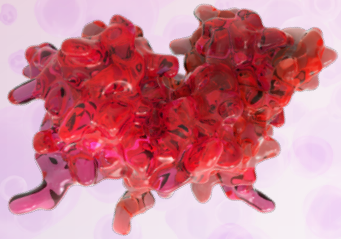


INTERFERON GAMMA (IFNγ)

A key player in the cytokine storm of primary hemophagocytic lymphohistiocytosis (HLH)[1,2]

Indication and Usage

Gamifant® (emapalumab-lzsg) is an interferon gamma (IFNγ)–blocking 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.

Important Safety Information

Before initiating Gamifant, patients should be evaluated for infection, including latent tuberculosis (TB). Prophylaxis for TB should be administered to patients who are at risk for TB or known to have a positive purified protein derivative (PPD) test result or positive IFNγ release assay.

Please see full Important Safety Information on page 5 and enclosed full Prescribing Information.

gamifant®
emapalumab-lzsg

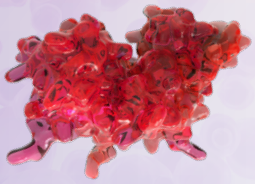
PRIMARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH):

A condition of life-threatening hyperinflammation[3]

A rare genetic disorder, primary HLH is characterized by a pathological, unregulated cytokine-mediated hyperinflammation that results in life-threatening multiorgan dysfunction.[4] Primary HLH typically occurs in infancy and early childhood, although teen and adult cases have also been identified.[3,5] Without treatment, **median survival of patients is less than 2 months** from a diagnosis of primary HLH, making it critical to initiate therapy quickly so as to manage the hyperinflammatory state caused by this cytokine "storm."[3]

A HEALTHY IMMUNE EXPRESSION OF IFNγ

IFNγ is a proinflammatory cytokine that plays a key role in cell communication during a healthy immune response to infections.[2,6-8] It can be produced by a variety of immune cells, including CD4+ T-helper type 1 (TH1) cells, activated CD8+ T cells, natural killer (NK) cells, natural killer T (NKT) cells, and antigen–presenting cells (APCs).[8,9]



INNATE IMMUNE RESPONSES

IFNγ helps eliminate intracellular pathogens by activating macrophages and NK cells.[9]

ADAPTIVE IMMUNE RESPONSES

IFNγ is responsible for both the differentiation and proliferation of T cells.[9]

IFNγ DRIVES HYPERINFLAMMATION TO CREATE THE CYTOKINE STORM[1,2]

While IFNγ is not the only cytokine that contributes to primary HLH, it does play a pivotal role in the pathogenesis of the disease.[2] Nonclinical data suggests that elevated IFNγ is responsible for the downstream release of other cytokines.[1,5] In primary HLH, the normal IFNγ pathway is compromised due to genetic mutations.[4,10]

Important Safety Information

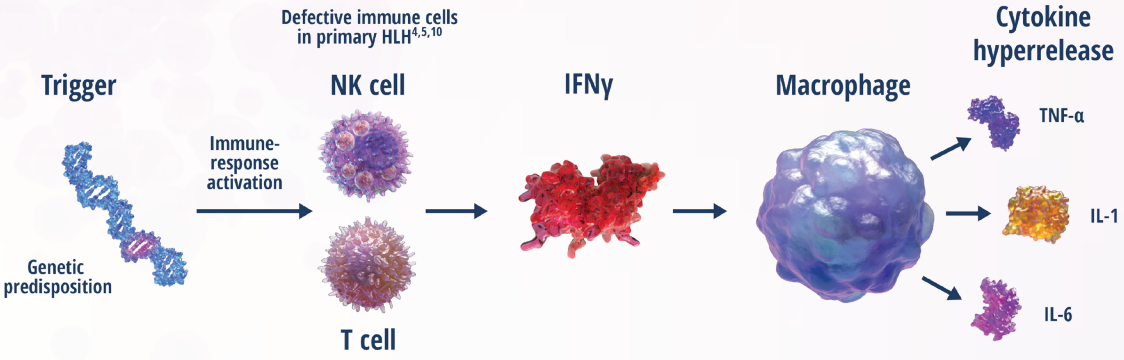
During Gamifant treatment, patients should be monitored for TB, adenovirus, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) every 2 weeks and as clinically indicated.

Patients should be administered prophylaxis for herpes zoster, *Pneumocystis jirovecii*, and fungal infections prior to Gamifant administration.

UPSTREAM ACTIVATION OF THE CYTOKINE STORM

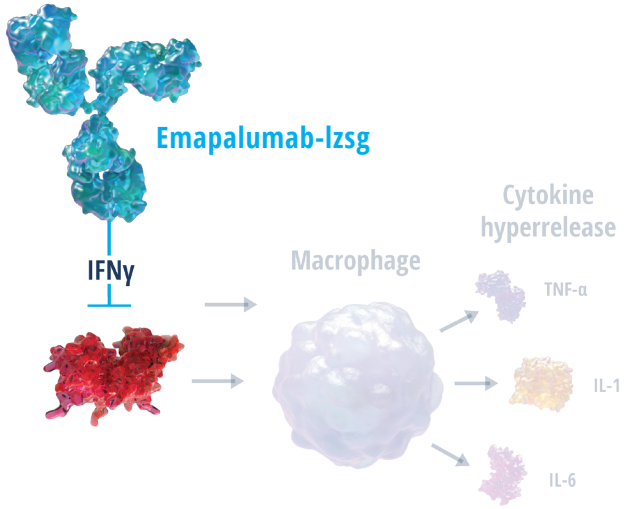
A possible consequence of these genetic mutations is excessive T-cell proliferation and corresponding overexpression of IFNγ which drives the activation of macrophages and may result in the phagocytosis of blood cells.[2,5]

At the same time, the release of additional proinflammatory molecules contributes to downstream hypercytokinemia. This cytokine "storm," in turn, leads to the life-threatening symptoms of primary HLH.[1,2,5]



Gamifant® (emapalumab-lzsg) targets IFNγ overexpression to subdue the cytokine storm[1,5]

Gamifant is a monoclonal antibody that binds to soluble and receptor-bound forms of IFNγ to neutralize its activity, blocking its intracellular signaling to inhibit macrophage activation and the downstream release of proinflammatory cytokines.[1,2,4,5,10,11]



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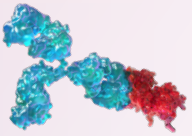
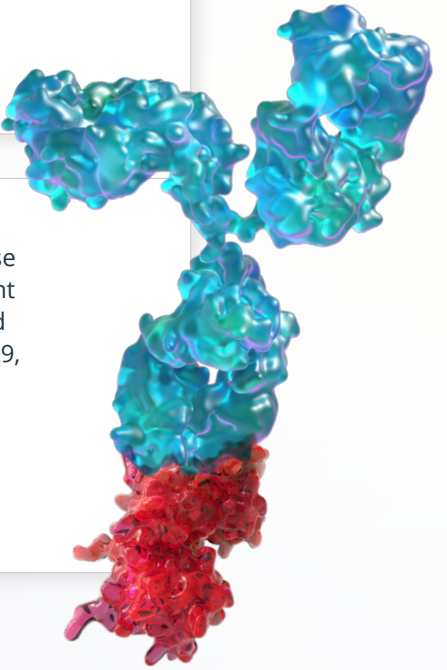
gamifant® emapalumab-lzsg

Gamifant® (emapalumab-lzsg), is the *first and only* FDA-approved treatment specifically developed for primary HLH[1,12]



The immediate treatment goal in primary HLH patients is to quickly bring the hyperinflammation under control.[3,10,13] In a departure from conventional, immunosuppressive therapies, Gamifant uniquely targets IFNγ to limit overexpression and subdube the hyperinflammatory symptoms of primary HLH.[1,2,5,10-12]

Watch a video simulation of IFNγ suppression with Gamifant. Gamifant.com/MOA



The only FDA-approved therapy for patients with refractory, recurrent, or progressive disease or intolerance to conventional therapy, Gamifant has been proven to cause a rapid and sustained reduction in the plasma concentrations of CXCL9, a chemokine induced by IFNγ.[1,2,5,10-12]

Explore clinical trial data to see how Gamifant might fit in to your practice. Gamifant.com/Trial

Important Safety Information

Indication and Usage

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Do not administer live or live attenuated vaccines to patients receiving Gamifant and for at least 4 weeks after the last dose of Gamifant. The safety of immunization with live vaccines during or following Gamifant therapy has not been studied.

Infusion-Related Reactions

Infusion-related reactions, including drug eruption, pyrexia, rash, erythema, and hyperhidrosis, were reported with Gamifant treatment in 27% of patients. In one-third of these patients, the infusion-related reaction occurred during the first infusion.

Adverse Reactions

In the pivotal trial, the most commonly reported adverse reactions (≥10%) for Gamifant included infection (56%), hypertension (41%), infusion-related reactions (27%), pyrexia (24%), hypokalemia (15%), constipation (15%), rash (12%), abdominal pain (12%), CMV infection (12%), diarrhea (12%), lymphocytosis (12%), cough (12%), irritability (12%), tachycardia (12%), and tachypnea (12%).

Additional selected adverse reactions (all grades) that were reported in less than 10% of patients treated with Gamifant included vomiting, acute kidney injury, asthenia, bradycardia, dyspnea, gastrointestinal hemorrhage, epistaxis, and peripheral edema.

Please see the enclosed full Prescribing Information for Gamifant.

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WE'RE HERE TO ANSWER YOUR QUESTIONS

Find out more about the only FDA-approved therapy for patients with refractory, recurrent, or progressive primary HLH or intolerance to conventional therapy.

Gamifant Patient Support Services

833.597.6530

Important Safety Information

Do not administer live or live attenuated vaccines to patients receiving Gamifant and for at least 4 weeks after the last dose of Gamifant. The safety of immunization with live vaccines during or following Gamifant therapy has not been studied.

Please see full Important Safety Information on page 5 and enclosed full Prescribing Information.

References:

1. Gamifant [prescribing information]. Stockholm, Sweden: Swedish Orphan Biovitrum AB; 2018. **2.** Jordan M, Hildeman D, Kappler J, Marrack P. An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8+ T cells and interferon gamma are essential for the disorder. *Blood*. 2004;104(3):735-743. doi:10.1182/blood-2003-10-3413. **3.** Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood.* 2011;118(15):4041-4052. doi:10.1182/blood-2011-03 278127. **4.** Price B, Lines J, Lewis D, Holland N. Haemophagocytic lymphohistiocytosis: a fulminant syndrome associate with multiorgan failure and high mortality that frequently masquerades as sepsis and shock. *S Afr Med J.* 2014;104(6):401-406. doi:7196/samj.7810. **5.** Sepulveda F, de Saint Basile G. Hemophagocytic syndrome: primary forms and predisposing conditions. *Curr Opin Immunol.* 2017;49:20-26. **6.** 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. *Pharmaceuticals (Basel).* 2015;8(4):793-815. doi: 10.3390/ph8040793. **7.** Zaidi MR, Merlino G. The two faces of interferon-γ in cancer. *Clin Cancer Res.* 2011;17(19):6118-6124. doi: 10.1158/1078-0432.CCR-11-0482. **8.** Pestka S, Krause CD, Walter MR. Interferons, interferon-like cytokines, and their receptors. *Immunol Rev.* 2004;202:8-32. **9.** Wang H, Yang Y-G. The complex and central role of interferon-γ in graft-versus-host disease and graft-versus-tumor activity. Author manuscript published by the National Institutes of Health, Public Access, PMC March 1, 2015. Published in final edited form in: *Immunol Rev.* 2014; 258(1): 30-44. doi:10.1111/imr.12151. **10.** Morimoto A, Nakazawa Y, Ishii E. Hemophagocytic lymphohistiocytosis: pathogenesis, diagnosis, and management. *Pediatr Int.* 2016;58:817-825. doi:10.1111/ped.13064. **11.** Data on file. Stockholm, Sweden: Swedish Orphan Biovitrum AB. **12.** FDA approves first treatment specifically for patients with rare and life-threatening type of immune disease [news release]. Silver Spring, MD: Food and Drug Administration; November 20, 2018. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm626263.htm. Accessed June 11, 2019. **13.** George M. Hemophagocytic lymphohistiocytosis: review of etiologies and management. *J Blood Med.* 2014;5:69-86. http://dx.doi.org/10.2147/JBM.S46255.

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