gamifant®
emapalumab-lzsg

Gamifant® (emapalumab-lzsg) Product Monograph

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.

Please see Important Safety Information on page 23 and accompanying full Prescribing Information.

gamifant®
emapalumab-lzsg

Executive Summary

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening hyperinflammatory syndrome[1] caused by severe hypercytokinemia due to a highly activated, but ineffective, immune response.[2,3] HLH can be primary, which is caused by genetic mutations, or secondary, which is associated with infection, malignancy, or immune system disease.[1,4,5] Primary HLH is mostly seen in infancy and early childhood,[1,4] with a median age of syndrome onset of 5.1 months.[6] The disease is invariably fatal if untreated, with a median survival of less than 2 months after diagnosis.[1] The only cure for primary HLH is hematopoietic stem cell transplant (HSCT)[7,8]; however, the hyperinflammation needs to be controlled prior to transplant.[2] Currently, hyperinflammation is controlled through an induction therapy using nonspecific immunosuppressive and chemotherapy agents, such as etoposide + dexamethasone +/- cyclosporine, which are associated with significant toxicity and a high risk of treatment-related morbidity[8-10] and are not approved by the US Food and Drug Administration (FDA) to treat primary HLH.[11-13] Half of patients fail to reach HSCT due to inadequate response to current induction regimens.[9,10] There is mounting evidence supporting the pivotal pathogenic role of interferon gamma (IFNγ) in the development of both primary and secondary forms of HLH.[14-19] Until now, regimens to prepare for transplant did not target this underlying cause of hyperinflammation.

This monograph addresses the impact and management of primary HLH.

Gamifant® (emapalumab-lzsg) is an anti-IFNγ–blocking antibody indicated for the treatment of adult and pediatric (newborn and older) patients with primary HLH with refractory, recurrent, or progressive disease or who are intolerant of conventional HLH therapy.[20] Gamifant is the only FDA-approved drug specifically targeting HLH.[21] Gamifant counters overexpression of IFNγ, which is central to the pathogenesis of HLH. Gamifant binds, neutralizes, and blocks the signaling that leads to hyperinflammation.[20]

The efficacy of Gamifant was demonstrated in a multicenter, 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. Sixty-three percent of patients who had a median of 3 prior treatments achieved overall response and demonstrated a clinically and statistically significant reduction in primary HLH disease activity. Seventy percent of patients treated with Gamifant progressed to HSCT.[20]

Safety and tolerability of Gamifant were evaluated in 34 patients with previously treated and untreated primary HLH. The most commonly reported adverse reactions (ARs) in the pivotal trial were infections, hypertension, infusion-related reactions, and pyrexia. Serious ARs were reported in 53% of patients. One patient discontinued the drug due to disseminated histoplasmosis, which was not ruled out prior to the trial.[20,22]

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 positive purified protein derivative (PPD) test result or positive IFNγ release assay.

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

Please see additional Important Safety information on page 23 and accompanying full Prescribing Information.

gamifant®
emapalumab-lzsg

Table of Contents

Please see Important Safety Information on page 23 and accompanying full Prescribing Information.

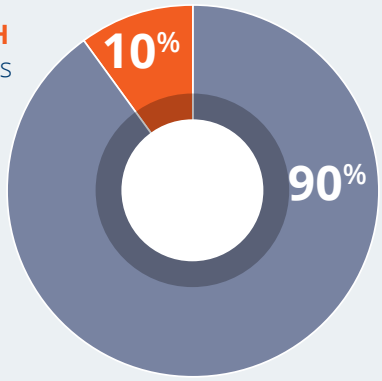
Overview of HLH

HLH: a rare, rapidly progressing, life-threatening immune disorder

- HLH is a rare, life-threatening hyperinflammatory syndrome[1] characterized by severe hypercytokinemia due to a highly activated, but ineffective, immune response[2,3]
  - The hyperinflammatory state associated with HLH causes the body's immune system to attack its own cells[1]
  - The dysfunctional immune response leads to a profound hypercytokinemia, which causes life-threatening organ damage and leaves patients vulnerable to deadly infections[1]

Two Types of HLH[1,2,5]

Primary (genetic/familial) HLH
Associated with genetic mutations



Secondary HLH
Associated with infection, malignancy, or immune system disease

Both primary and secondary HLH are clinically described by a dysregulation of the immune system leading to a profound hypercytokinemia with deleterious consequences on various tissues and organs.[1]

Please see Important Safety Information on page 23 and accompanying full Prescribing Information.

Overview of HLH *(continued)*

Characteristics of primary HLH

- Primary or familial HLH is a heterogeneous autosomal recessive disorder characterized by a severe impairment or absence of cytotoxic function by natural killer (NK) and CD8+ T cells with striking activation of the immune system[1,4,5,23]
- Primary HLH is ultra-rare and often affects infants and children[4,6]
  - Approximately 80 pediatric patients were diagnosed with primary HLH in the United States in 2017[22]

5.1 months
Median age of onset[6]

Median survival if untreated <2 months
after diagnosis.
Disease is invariably fatal if untreated[1]

Primary HLH presents as a medical emergency, with life-threatening, nonspecific symptoms[24,25]

- Primary HLH syndromes are subclassified into familial hemophagocytic lymphohistiocytosis (FHL)-1 through FHL-5, based on anomalies in proteins and genetic mutations[1]

Genetic Defects in Primary HLH[1]

FHL Subclass	Chromosome	Gene	Gene Function	Protein
FHL-1	9q21.3-q22	Unknown	Unknown	Unknown
FHL-2	10q21-22	*PFR1*	Induction of apoptosis	Perforin
FHL-3	17q25	*UNC13D*	Vesicle priming	Munc13-4
FHL-4	6q24	*STX11*	Vesicle transport	Syntaxin11
FHL-5	19p13.2-3	*STXBP2 (UNC18B)*	Vesicle transport	Munc18-2
Other HLH-Associated Diseases				
CHS-1	1q42.1-q42.2	*LYST*	Vesicle transport	Lyst
GS-2	15q21	*RAB27A*	Vesicle transport	Rab27a
XLP-1	Xq25	*SH2D1A*	Signal transduction and activation of lymphocytes	SAP
XLP-2	Xq25	*BIRC4*	Various signaling pathways	XIAP

- Although primary HLH is recognized as a disease that strikes predominantly in childhood, it is a condition that can be found in adults as well[1,26]
- Children with a defined genetic cause of HLH often have a secondary assault, such as an infection, that triggers HLH[1]

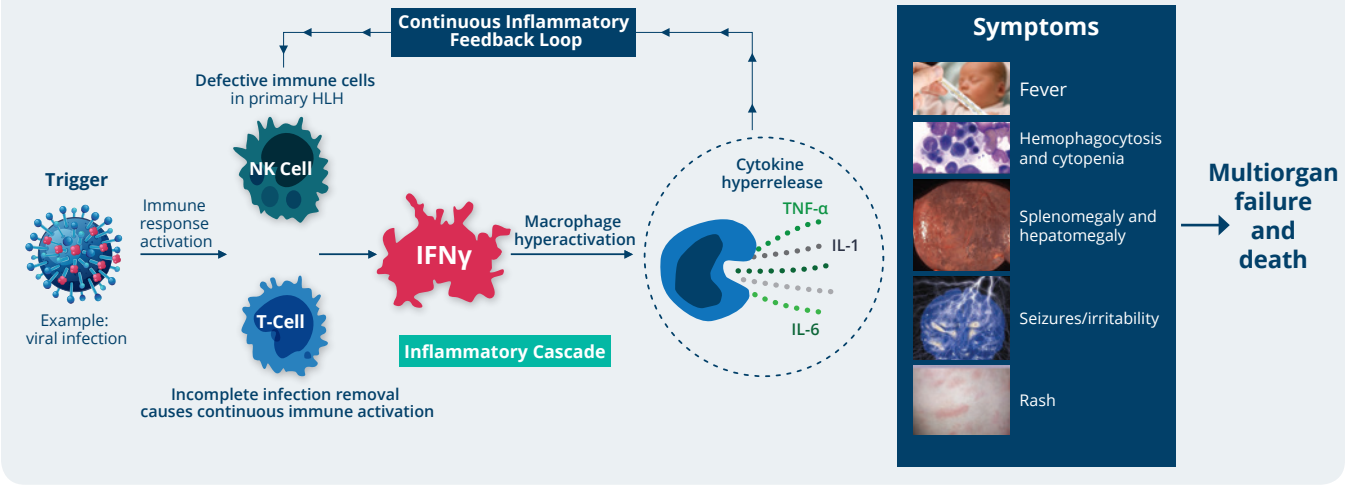
Please see Important Safety Information on page 23 and accompanying full Prescribing Information.

Overview of HLH *(continued)*

Immune dysregulation characterized by a cytokine storm causes HLH

- HLH is characterized by a cytokine storm that gives rise to the symptoms of the disease[4,17,26]
- When triggered by an event such as an infection, defective cytotoxic T cells and NK cells are unable to remove the infection and secrete high amounts of IFNγ[17,27,28]
- Stimulation of macrophages by IFNγ results in the release of other cytokines by these cells, including interleukin (IL)-6, tumor necrosis factor (TNF)-alpha, and IL-10. This creates a "feedback loop" that reactivates immune cells, leading to a continuous inflammatory cascade[17,27,28]
- Persistent immune activation results in massive overexpression of IFNγ that is central to the uncontrolled and often fatal release of inflammatory cytokines, resulting in a cytokine storm[17,26,28]
- Inflammatory cytokines act via different pathways to produce the symptoms characteristic of HLH.[17,26] If the hyperinflammatory reaction is not effectively controlled, HLH can rapidly proceed to multiple organ failure and death[29]

Cytokine Storm: Hyperinflammation Due to Persistent Immune Activation[17,26,28]



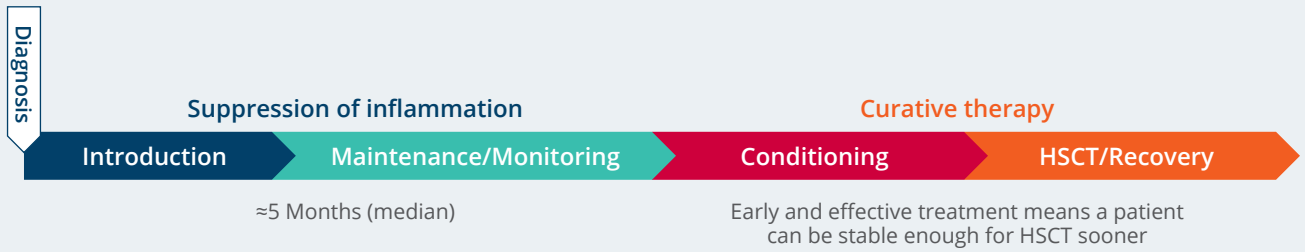
Please see Important Safety Information on page 23 and accompanying full Prescribing Information.

Overview of HLH *(continued)*

Current treatment guidelines for primary HLH

- HSCT is the only cure for primary HLH[7,8]
- There are currently no approved drugs for the treatment of primary HLH; however, experts in the field have established guidelines, the HLH-1994 and HLH-2004 protocols, for the management of patients with HLH[8-10]
- The treatment regimen for primary HLH consists of 3 phases: induction, maintenance, and conditioning + HSCT[2]

The Treatment Pathway[2,9,30]



- After clinical diagnosis, patients receive induction therapy, which until now consisted of nonspecific immunosuppressive and chemotherapy agents, such as etoposide + dexamethasone +/- cyclosporine[8-10]

The main goal of the induction therapy is to suppress the life-threatening inflammatory process that characterizes primary HLH, enabling HSCT as quickly as possible[9,10]

- A shorter time to transplant results in a better prognosis for survival

- Despite the adoption of the HLH 1994/2004 protocols, no significant improvement in mortality rates has been observed for primary HLH during the past 20 years[9]
- Poor primary HLH control is associated with higher transplant-related mortality,[31] underscoring the need for effective therapies that can improve eligibility and survival rates for HSCT

Please see Important Safety Information on page 23 and accompanying full Prescribing Information.

Overview of HLH *(continued)*

Unmet need

- Until now, induction therapy drugs were nonspecific and carried significant short- and long-term toxicities that may become life-threatening[8-10]
  - They do not target the massive overexpression of IFNγ that is central to the cytokine storm[4]
  - They may be associated with severe infections, neutropenia, posterior reversible encephalopathy syndrome, and renal toxicity[10,31]
- About half of patients with primary HLH do not achieve HSCT due to[9,10]
  - Insufficient response
  - Intolerance
  - Being refractory to treatment

50% **of patients fail to reach HSCT due to an inadequate response to current induction regimens**[9,10]

Please see Important Safety Information on page 23 and accompanying full Prescribing Information.

gamifant®
emapalumab-lzsg

About Gamifant (emaplumab-lzsg)

Indication for use

Gamifant is an IFNγ-blocking antibody indicated 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.[20]

Mechanism of action

- Gamifant is a monoclonal antibody that binds to and neutralizes IFNγ[20]
- Nonclinical data suggest that IFNγ plays a pivotal role in the pathogenesis of HLH by being hypersecreted[20]

Dosage and administration

Recommended Dosing[20]

Starting Dose	• 1 mg/kg intravenously infused over 1 hour
Frequency	• Twice per week (every 3 or 4 days) • Until HSCT is performed or unacceptable toxicity
Titration	• May be increased to 3 mg/kg on day 3, then to 6 mg/kg on day 6, and up to a maximum dose of 10 mg/kg on day 9 • Based on physician's assessment of clinical and laboratory criteria

- Discontinue Gamifant when a patient no longer requires therapy for the treatment of HLH[20]

Premedications and concomitant medication information

Premedications[20]	• Administer prophylaxis for herpes zoster, *Pneumocystis jirovecii*, and fungal infections prior to Gamifant administration
Frequency[20]	• Administer dexamethasone at a daily dose of at least 5 to 10 mg/m^2 the day before Gamifant treatment begins • In patients who were receiving baseline dexamethasone, they may continue their regular dose provided it is at least 5 mg/m^2 • Dexamethasone can be tapered according to the judgment of the treating physician

Important Safety Information *(continued)*

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

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 additional Important Safety Information on page 23 and accompanying full Prescribing Information.

gamifant®
emapalumab-lzsg

About Gamifant (emapalumab-lzsg) *(continued)*

Monitoring to assess safety

Before and During Gamifant Treatment[20]	
Before Initiating Gamifant Treatment	• Test for latent tuberculosis infections using the purified protein derivative (PPD) or IFNγ release assay • Evaluate patients for tuberculosis risk factors • Administer tuberculosis prophylaxis to patients at risk for tuberculosis or who have a positive PPD test result or positive IFNγ release assay
During Gamifant Treatment	• Monitor for tuberculosis, adenovirus, EBV, and CMV every 2 weeks and as clinically indicated

CMV=cytomegalovirus; EBV= Epstein-Barr virus.

Important Safety Information *(continued)*

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.

Please see additional Important Safety Information on page 23 and accompanying full Prescribing Information.

gamifant®
emapalumab-lzsg

About Gamifant (emapalumab-lzsg) *(continued)*

Dose modification based on response

- The Gamifant dose may be titrated up if disease response is unsatisfactory. After the patient's clinical condition is stabilized, decrease the dose to the previous level to maintain clinical response[20]

Dose Titration Criteria[20]

Treatment Day	Gamifant Dose	Criteria for Dose Increase
Day 1	Starting dose of 1 mg/kg	Not applicable
On Day 3	Increase to 3 mg/kg	Unsatisfactory improvement in clinical condition, as assessed by a health care provider *and* at least 1 of the following: • Fever – persistent or recurrent • Platelet count – If baseline <50,000/mm^3 and no improvement to >50,000/mm^3 – If baseline >50,000/mm^3 and <30% improvement – If baseline >100,000/mm^3, any decrease to <100,000/mm^3 • Neutrophil count – If baseline <500/mm^3 and no improvement to >500/mm^3 – If baseline >500-1000/mm^3 and decrease to <500/mm^3 – If baseline 1000-1500/mm^3 and decrease to <1000/mm^3 • Ferritin – If baseline ≥3000 ng/mL and <20% decrease – If baseline <3000 ng/mL and any increase to >3000 ng/mL • Splenomegaly – any worsening • Coagulopathy (both D-dimer and fibrinogen must apply) – D-dimer • If abnormal at baseline and no improvement – Fibrinogen • If baseline levels ≤100 mg/dL and no improvement • If baseline levels >100 mg/dL and any decrease to <100 mg/dL
From Day 6 on	Increase to 6 mg/kg	
From Day 9 on	Increase to 10 mg/kg	Assessment by a health care provider that based on initial signs of response, a further increase in Gamifant dose can be of benefit

Important Safety Information *(continued)*

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%).

Please see additional Important Safety Information on page 23 and accompanying full Prescribing Information.

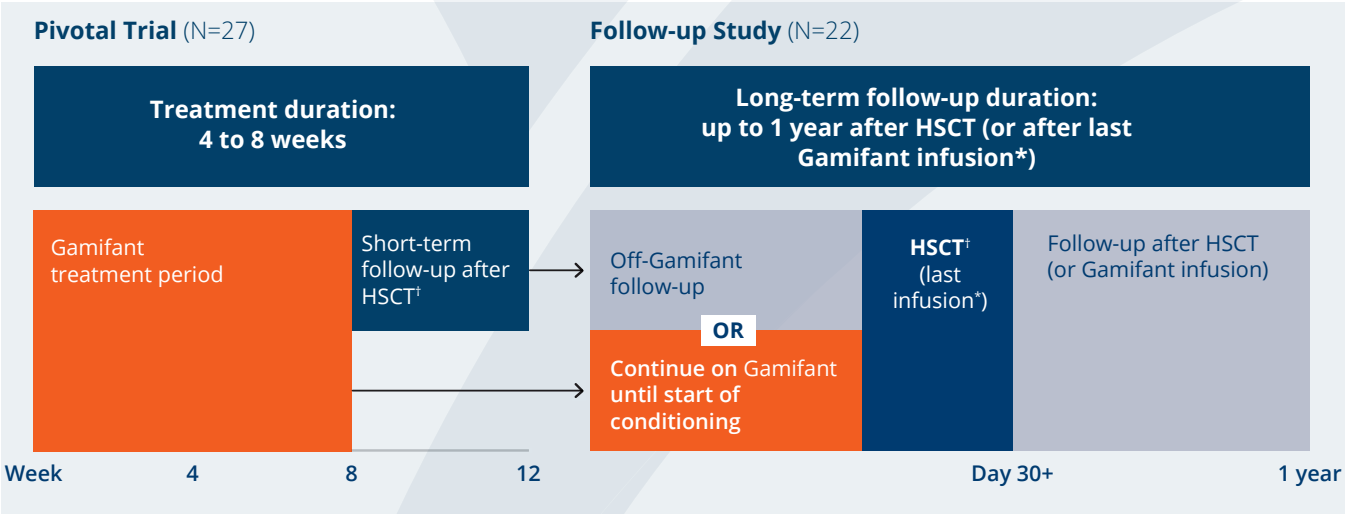
gamifant®
emapalumab-lzsg

Pivotal Clinical Trial

Study design

- The efficacy of Gamifant (emapalumab-lzsg) was evaluated in a multicenter, open-label, single-arm trial (NI-0501-04; NCT01818492) in 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[20]
  - Twenty-seven patients enrolled and received treatment for 4 to 8 weeks in the study and 20 patients (74%) completed the study. Seven patients (26%) were prematurely withdrawn[20,22]
  - Twenty-two patients (81%) enrolled in the open-label extension study, which monitored patients for up to 1 year after HSCT or after the last Gamifant infusion (NI-0501-05; NCT02069899)[20]

Pivotal Trial Study Design[20,22]



*Last infusion for patients who do not undergo HSCT.
†HSCT may occur either in the pivotal trial or follow-up study.

- All patients received dexamethasone as background HLH treatment with doses of between 5 mg/m^2 and 10 mg/m^2 per day[20]
- Gamifant was administered at a starting dose of 1 mg/kg every 3 days with subsequent dose increases up to 10 mg/kg based on clinical and laboratory parameters interpreted as an unsatisfactory response[20]
  - Forty-four percent of patients remained at a dose of 1 mg/kg, 30% of patients increased to 3 mg/kg to 4 mg/kg, and 26% of patients increased to 6 mg/kg to 10 mg/kg
  - The median time to dose increase was 27 days (range: 3-31 days)
  - Twenty-two percent of patients required a dose increase in the first week of treatment

Important Safety Information *(continued)*

Adverse Reactions *(continued)*

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, gastro-intestinal hemorrhage, epistaxis, and peripheral edema.

Please see additional Important Safety Information on page 23 and accompanying full Prescribing Information.

gamifant®
emapalumab-lzsg

Pivotal Clinical Trial *(continued)*

Study eligibility

Inclusion Criteria[20,22]

Males or females ≤18 years old

Fulfillment of 5 of 8 of the following criteria:

- Fever
- Splenomegaly
- Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood)
  - Hemoglobin <90 g/L (in infants <4 weeks: hemoglobin <100 g/L)
  - Platelets <100 ×10^9/L
  - Neutrophils <1× 10^9/L
- Hypertriglyceridemia (fasting, ≥265 mg/100 mL) and/or hypofibrinogenemia (≤1.5 g/L)
- Hemophagocytosis in bone marrow, spleen, or lymph nodes
- Ferritin ≥500 µg/mL
- Low or absent NK cell activity
- Soluble CD25 (soluble IL-2 receptor) >2400 U/mL (or per local reference laboratory)

OR

Molecular diagnosis consistent with primary HLH
Pathologic mutations of *PRF1*, *UNC13D*, and *STX11* identified

OR

Family history consistent with primary HLH

Patients having already received HLH conventional therapy must have fulfilled 1 of the following criteria as assessed by the treating physician:

- No or inadequate response
- Failure to maintain satisfactory response
- Intolerance of treatment

Exclusion Criteria[22]

- Secondary HLH consequent to a proven rheumatic or neoplastic disease
- HLH associated with active mycobacteria, *Histoplasma capsulatum*, *Shigella*, *Campylobacter*, *Leishmania*, or *Salmonella* infections
- Evidence of past history of tuberculosis or of latent tuberculosis
- Presence of a malignancy
- Concomitant disease or malformation severely affecting cardiovascular, pulmonary, liver, or renal function
- Body weight <3 kg
- Patients treated with T-cell depleting agents (eg, ATG, anti-CD52) within the 2 weeks prior to screening, or any other biologic drug within 5 times their defined half-life period (excluding rituximab for documented B-cell EBV)
- Positive serology for HIV antibodies, hepatitis B surface antigen, or hepatitis C antibodies
- Vaccination with a live or attenuated live vaccine within the previous 12 weeks prior to screening
- Pregnant or lactating female patients

Important Safety Information *(continued)*

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 positive purified protein derivative (PPD) test result or positive IFNγ release assay.

Please see additional Important Safety Information on page 23 and accompanying full Prescribing Information.

gamifant®
emapalumab-lzsg

Pivotal Clinical Trial *(continued)*

Study endpoints

Primary and Secondary Efficacy Endpoints

Primary Efficacy Endpoint[20]	Secondary Efficacy Endpoints[22]
• Overall response rate (ORR), defined as complete response or partial response or HLH improvement at the end of treatment	• Time to response any time during the study • Durability of response or maintenance of response achieved any time during the study until the end of treatment • Number of patients who proceeded to HSCT, when deemed indicated

- ORR was evaluated using an algorithm that included the following objective clinical and laboratory parameters: fever, splenomegaly, central nervous system (CNS) symptoms, complete blood count, fibrinogen and/or D-dimer, ferritin, and soluble CD25 (also referred to as soluble IL-2 receptor) levels[20]

Definitions of Response[20,22]

Complete Response (CR)	• No fever (body temperature <37.5°C) • Normal spleen size as measured by 3D abdominal ultrasound • No cytopenia (absolute neutrophil count ≥1.0 x 10^9/L and platelet count ≥100 x 10^9/L with absence of G-CSF and transfusion support must be documented for ≥4 days) • No hyperferritinemia (serum level <2000 µg/L) • No evidence of coagulopathy (normal D-dimer and/or normal [>150 mg/dL] fibrinogen levels) • No neurological and CSF abnormalities attributed to HLH • No sustained worsening of soluble CD25 (as indicated by ≥2 consecutive measurements that were >2-fold higher than baseline)
Partial Response (PR)	• ≥3 of the HLH clinical and laboratory abnormalities (including CNS abnormalities) met the aforementioned criteria for CR • In the case of "reactivated patients" who entered the study with 3 abnormal HLH features, ≥2 criteria were to meet the definition given • There was no progression of other aspects of HLH disease pathology
HLH Improvement	• Improvement (>50% change from baseline) of ≥3 HLH clinical and laboratory abnormalities (including CNS involvement) • In the case of "reactivated patients" who entered the study with 2 abnormal HLH features, a change from baseline greater than 50% for both defined HLH as improved

CSF=cerebral spinal fluid; G-CSF=granulocyte-colony stimulating factor.

Important Safety Information *(continued)*

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

Please see additional Important Safety Information on page 23 and accompanying full Prescribing Information.

gamifant®
emapalumab-lzsg

Pivotal Clinical Trial *(continued)*

Patient demographics

Patient Demographic Characteristics[20,22]

Parameter		**Gamifant** (N=27)
Age at Parental/Family Informed Consent (years)		2.55 (3.231) Mean (SD) 1.00 Median 0.2, 13.0 Min, Max
Age Category n (%)	<2 years	15 (55.6)
	≥2 to <12 years	11 (40.7)
	≥12 to <18 years	1 (3.7)
Sex n (%)	Female	16 (59.3)
	Male	11 (40.7)
Race n (%)	White	17 (63.0)
	Asian	3 (11.1)
	African descent	3 (11.1)
	Mixed/multiracial	0
	Other	4 (14.8)
Country of Origin n (%)	US	7 (25.9)
	Italy	3 (11.1)
	Others	12 (44.5)
	Missing	5 (18.5)

- A genetic mutation known to cause HLH was present in 82% of patients. The most frequent causative mutations were FHL3-UNC13D (MUNC 13-4) (26%), FHL3-PRF1 (19%), and Griscelli Syndrome type 2 (19%)[20]
- Patients received a median of 3 prior agents before enrollment into the trial[20]
  - Prior regimens included combinations of the following agents: dexamethasone, etoposide, cyclosporine A, and antithymocyte globulin
- At baseline, 78% of patients had elevated ferritin levels, thrombocytopenia (70% with platelet count of <100 x 10^9 cells/L), hypertriglyceridemia (67% with triglyceride level >3 mmol/L)[20]
  - Thirty-seven percent of patients had CNS findings
  - Forty-one percent of patients had active infections not due to specific pathogens favored by IFNγ neutralization at the time of Gamifant infusion

Important Safety Information *(continued)*

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

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 additional Important Safety Information on page 23 and accompanying full Prescribing Information.

gamifant®
emapalumab-lzsg

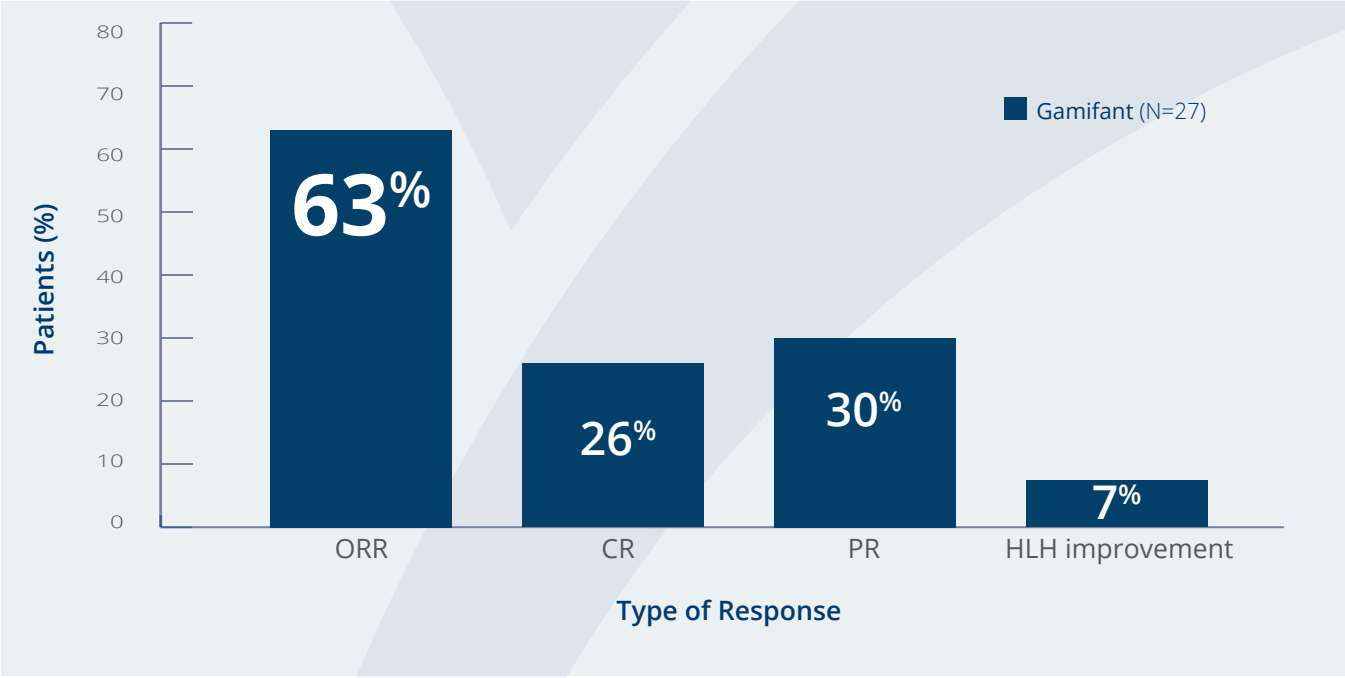
Pivotal Clinical Trial *(continued)*

Clinical efficacy

Primary Endpoint: ORR

- Gamifant (emapalumab-lzsg) demonstrated significant reduction in HLH disease activity
  - Gamifant met the primary endpoint through the induction of a clinically and statistically significant overall response in 63% (95% CI: 0.42, 0.81) of patients with primary HLH[20]

ORR at End of Treatment[20]



Important Safety Information *(continued)*

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.

Please see additional Important Safety Information on page 23 and accompanying full Prescribing Information.

gamifant®
emapalumab-lzsg

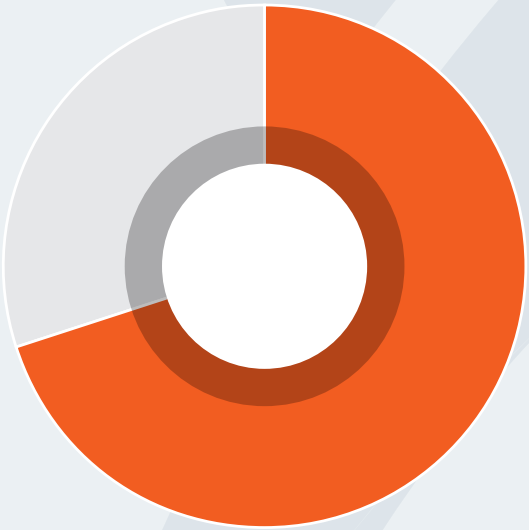
Pivotal Clinical Trial *(continued)*

Clinical efficacy *(continued)*

Secondary Endpoints

- Most patients progressed to HSCT after Gamifant treatment[20]
  - Seventy percent of patients (19/27) proceeded to HSCT[20]
  - Median duration of treatment with Gamifant prior to HSCT was 59 days[20]
  - Of those who proceeded to HSCT, 89.5% (17/19) engrafted[22]

Patients Who Proceeded to HSCT[20]



70%
Proceed to HSCT

- The median duration of response, defined as time to loss of first response, was not reached (range: 4 to >56 days)[20]

Important Safety Information *(continued)*

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, gastro-intestinal hemorrhage, epistaxis, and peripheral edema.

Please see additional Important Safety Information on page 23 and accompanying full Prescribing Information.

gamifant®
emapalumab-lzsg

Gamifant (emapalumab-lzsg) Safety and Tolerability

Adverse reactions (ARs) with Gamifant

- The safety profile for Gamifant was derived from 34 patients with untreated primary HLH and previously treated patients with primary HLH (NCT01818492)[20]
- The most commonly reported ARs (≥20%) were infections, hypertension, infusion-related reactions, and pyrexia[20]

ARs Reported in ≥10% of Patients in the Pivotal Trial[20]

Adverse Reactions	**Gamifant** (N=34) (%)	Adverse Reactions	**Gamifant** (N=34) (%)
Infections*	56	Abdominal pain	12
Hypertension†	41	CMV infection	12
Infusion-related reactions‡	27	Diarrhea	12
Pyrexia	24	Lymphocytosis	12
Hypokalemia	15	Cough	12
Constipation	15	Irritability	12
Rash	12	Tachycardia	12
		Tachypnea	12

*Includes viral, bacterial, and fungal infections, and infections for which no pathogen was identified.
†Includes secondary hypertension.
‡Includes events of drug eruption, pyrexia, rash, erythema, and hyperhidrosis.

- Additional selected ARs (all grades) that were reported in less <10% of patients treated with Gamifant included vomiting, acute kidney injury, asthenia, bradycardia, dyspnea, gastrointestinal hemorrhage, epistaxis, and peripheral edema[20]
- Mild to moderate infusion-related reactions, including drug eruption, pyrexia, rash, erythema, and hyperhidrosis, were observed in 27% of patients[20]
- Serious infections, such as sepsis, pneumonia, bacteremia, disseminated histoplasmosis, necrotizing fasciitis, viral infections, and perforated appendicitis, were observed in 32% of patients[20]
- Serious ARs were reported in 53% of patients. The most common serious ARs (≥3%) included infections, gastrointestinal hemorrhage, and multiple organ dysfunction[20]
- Only 1 patient discontinued treatment due to an AR—disseminated histoplasmosis, which was not ruled out prior to trial initiation[20,22]

Please see additional Important Safety Information on page 23 and accompanying full Prescribing Information.

gamifant®
emapalumab-lzsg

Gamifant (emapalumab-lzsg) Safety and Tolerability *(continued)*

Immunogenicity

- Of the 64 subjects evaluated for antitherapeutic antibodies (ATAs) to Gamifant, ATAs were detected in 3 subjects (5%)[20]
- Treatment-emergent ATAs with neutralizing ability were detected in 1 out of 33 patients (3%) in the primary HLH clinical trial. One patient receiving Gamifant through compassionate use developed transient nonneutralizing treatment-emergent ATAs[20]
  - In both of these patients, ATAs occurred within the first 9 weeks following the initiation of Gamifant treatment[20]
- In addition, 1 healthy subject tested positive for ATAs following a single dose of Gamifant. No evidence of an altered safety or efficacy were observed in the patients who developed ATAs[20]

Drug interactions

- The formation of cytochrome P450 (CYP450) enzymes may be suppressed by increased levels of cytokines (such as IFNγ) during chronic inflammation[20]
- Gamifant, through neutralization of IFNγ, may normalize CYP450 activities, which may reduce the efficacy of drugs that are CYP450 substrates due to increased metabolism[20]

Please see additional Important Safety Information on page 23 and accompanying full Prescribing Information.

gamifant®
emapalumab-lzsg

Use in Specific Populations

Pregnancy

- There are no available data on Gamifant (emapalumab-lzsg) use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. In an animal reproduction study, a murine surrogate anti-mouse IFNγ antibody administered to pregnant mice throughout gestation crossed the placental barrier and no fetal harm was observed[20]

Lactation

- There is no information regarding the presence of emapalumab-lzsg in human milk, the effects on the breastfed child, or the effects on milk production. Published data suggest that only limited amounts of therapeutic antibodies are found in breast milk and they do not enter the neonatal and infant circulations in substantial amounts[20]
- The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Gamifant and any potential adverse effects on the breastfed child from Gamifant or from the underlying maternal condition[20]

Pediatric use

- The safety and effectiveness of Gamifant were demonstrated in pediatric patients, newborn and older, with primary HLH that was reactivated or refractory to conventional therapies. Use of Gamifant is supported by a single-arm trial in 27 pediatric patients with reactivated or refractory primary HLH. This study included pediatric patients in the following age groups: 5 patients aged newborn to 6 months, 10 patients aged 6 months to 2 years, and 12 patients aged 2 years to 13 years[20]

Geriatric use

- Clinical studies of Gamifant did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients[20]

Important Safety Information *(continued)*

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 positive purified protein derivative (PPD) test result or positive IFNγ release assay.

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

Please see additional Important Safety Information on page 23 and accompanying full Prescribing Information.

gamifant®
emapalumab-lzsg

Summary

- Primary HLH is an ultra-rare, rapidly progressive, often fatal disease that typically occurs in infancy and early childhood.[1,4,5] Current induction treatment protocols are nonspecific, aggressive, and may be toxic[8-10] with more than half of patients failing to achieve HSCT,[9] the only chance at cure for primary HLH[7,8]
- Gamifant (emapalumab-lzsg) is the first drug to be specifically developed for HLH and the only drug currently approved for the treatment of adult and pediatric (newborn and older) patients with primary HLH with refractory, recurrent, or progressive disease or who are intolerant of conventional HLH therapy[20,21]
- Gamifant demonstrated clinically and statistically significant overall response in 63% of patients through the achievement of CR, PR, or HLH improvement[20]
- Seventy percent of previously treated patients proceeded to HSCT with Gamifant treatment[20]
- The median duration of treatment with Gamifant was 59 days[20]
- In the number of patients who were evaluated for safety
  - The most commonly reported ARs (≥20%) were infections, hypertension, infusion-related reactions, and pyrexia[20]
  - Twenty-seven percent of patients had mild to moderate infusion-related reactions and 32% of patients had serious infections[20]
  - Serious ARs were reported in 53% of patients and only 1 patient discontinued due to treatment-related AR[20]

Important Safety Information *(continued)*

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

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 additional Important Safety Information on page 23 and accompanying full Prescribing Information.

gamifant®
emapalumab-lzsg

References:

1. George MR. Hemophagocytic lymphohistiocytosis: review of etiologies and management. *J Blood Med*. 2014;5:69-86.
2. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood*. 2011;118(15):4041-4052.
3. Farkas J. PulmCrit- Sepsis 4.0: Understanding sepsis - HLH overlap syndrome. https://emcrit.org/pulmcrit/sepsis-hlh-overlap-syndrome-shlhos/. Published June 6, 2016. Accessed October 26, 2018.
4. El Hachem G. Hemophagocytic lymphohistiocytosis, a syndrome of excessive immune activation: review of the literature. *J Hematol Mult Myeloma*. 2017;1(1):1002-1005.
5. Ishii E. Hemophagocytic lymphohistiocytosis in children: pathogenesis and treatment. *Front Pediatr*. 2016;4:47.
6. Esteban YM, de Jong JLO, Tesher MS. An overview of hemophagocytic lymphohistiocytosis. *Pediatr Ann*. 2017;46(8):e309-e313.
7. Henter J-I, Horne A, Aricò M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48(2):124-131.
8. Morimoto A, Nakazawa Y, Ishii E. Hemophagocytic lymphohistiocytosis: pathogenesis, diagnosis, and management. *Pediatr Int*. 2016;58(9):817-825.
9. Bergsten E, Horne A, Aricò 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):2728-2738.
10. Marsh RA, Haddad E. How I treat primary haemophagocytic lymphohistiocytosis. *Br J Haematol*. 2018;182(2):185-199.
11. Etoposide injection. MedLine Plus website. https://medlineplus.gov/druginfo/meds/a697011.html. Accessed October 3, 2018.
12. Dexamethasone. MedLine Plus website. https://medlineplus.gov/druginfo/meds/a682792.html. Accessed October 3, 2018.
13. Cyclosporine. MedLine Plus website. https://medlineplus.gov/druginfo/meds/a601207.html. Accessed October 3, 2018.
14. Behrens EM, Canna SW, Slade K, et al. Repeated TLR9 stimulation results in macrophage activation syndrome-like disease in mice. *J Clin Invest*. 2011;121(6):2264-2277.
15. Bracaglia C, de Graaf K, Pires Marafon D, et al. Elevated circulating levels of interferon-γ and interferon-γ-induced chemokines characterise patients with macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. *Ann Rheum Dis*. 2017;76(1):166-172.
16. Buatois V, Chatel L, Cons L, et al. Use of a mouse model to identify a blood biomarker for IFNγ activity in pediatric secondary hemophagocytic lymphohistiocytosis. *Transl Res*. 2017;180:37-52.e2.
17. Jordan MB, 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.
18. Pachlopnik Schmid J, Ho CH, Chrétien F, et al. Neutralization of IFNγ defeats haemophagocytosis in LCMV-infected perforin- and Rab27a-deficient mice. *EMBO Mol Med*. 2009;1(2):112-124.
19. Prencipe G, Caiello I, Pascarella A, et al. Neutralization of IFN-γ reverts clinical and laboratory features in a mouse model of macrophage activation syndrome. *J Allergy Clin Immunol*. 2018;141(4):1439-1449.
20. Gamifant [prescribing information]. Geneva, Switzerland: Novimmune SA; November 2018.
21. FDA approves Gamifant® (emapalumab), the first and only treatment for primary haemophagocytic lymphohistiocytosis (HLH) [news release]. Stockholm, Sweden: Sobi; November 20, 2018. https://www.sobi.com/en/investors/fda-approves-gamifantr-emapalumab-first-and-only-treatment-primary-haemophagocytic. Accessed November 20, 2018.
22. Data on file. Sobi, Inc.
23. Brisse E, Matthys P, Wouters CH. Understanding the spectrum of haemophagocytic lymphohistiocytosis: update on diagnostic challenges and therapeutic options. *Br J Haematol*. 2016;174(2):175-187.
24. Price B, Lines J, Lewis D, Holland N. Haemophagocytic lymphohistiocytosis: a fulminant syndrome associated with multiorgan failure and high mortality that frequently masquerades as sepsis and shock. *S Afr Med J*. 2014;104(6):401-406.
25. Siddaiahgari SR, Agarwal S, Madukuri P, Moodahadu LS. Hemophagocytic lymphohistiocytosis: a review. *J Blood Disord Transfus*. 2016;7:363. doi:10.4172/2155-9864.1000363.
26. Chandrakasan S, Filipovich AH. Hemophagocytic lymphohistiocytosis: advances in pathophysiology, diagnosis, and treatment. *J Pediatr*. 2013;163(5):1253-1259.
27. Schulert GS, Grom AA. Pathogenesis of macrophage activation syndrome and potential for cytokine-directed therapies. *Annu Rev Med*. 2015;66:145-159.
28. Vizcaino MA, Eberhart CG, Rodriguez FJ. Hemophagocytic lymphohistiocytosis in adults with intraocular involvement: clinicopathologic features of 3 cases. *Ocul Oncol Pathol*. 2017;4(1):1-11.
29. Gholam C, Grigoriadou S, Gilmour KC, Gaspar HB. Familial haemophagocytic lymphohistiocytosis: advances in the genetic basis, diagnosis and management. *Clin Exp Immunol*. 2011;163(3):271-283.
30. Henter J-I, Samuelsson-Horne A, Aricò M, et al; for the Histiocyte Society. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. *Blood*. 2002;100(7):2367-2373.
31. Trottestam H, Horne A, Aricò M, et al. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. *Blood*. 2011;118(17):4577-4584

Please see Important Safety information on page 23 and accompanying full Prescribing Information.

gamifant®
emapalumab-lzsg

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 positive purified protein derivative (PPD) test result or positive IFNγ release assay.

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.

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, gastro-intestinal hemorrhage, epistaxis, and peripheral edema.

Please see the full Prescribing Information for Gamifant.

sobi