gamifant®
emapalumab-lzsg

Guide to Gamifant

Dosing and Administration

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Gamifant
Dosing and Administration

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Indication and Important Safety Information

Indication

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

Infections

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.

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.

Increased Risk of Infection With Use of Live Vaccines

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.

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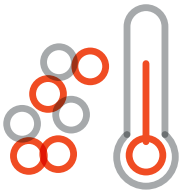
About primary HLH

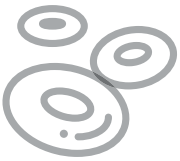
Primary HLH is a genetic disorder that typically occurs in infancy and early childhood, manifesting mostly during the first year of life, but may also occur in teens and adults.[1,2]

Primary HLH presents as a heterogeneous syndrome of rapidly progressive, life-threatening symptoms that can quickly become fatal unless diagnosed and treated. Common symptoms may include[1,3,4]:



- Fever
- Infection
- Rash

- Hepatosplenomegaly
- Liver impairment
- Jaundiced appearance



- Hyperferritinemia
- Coagulation defects
- Severe cytopenia

- Seizure

- Pulmonary dysfunction

Massive overexpression of IFNγ is central to the "cytokine storm," the uncontrolled release of inflammatory cytokines and overactivation of phagocytes that give the syndrome its name[5]

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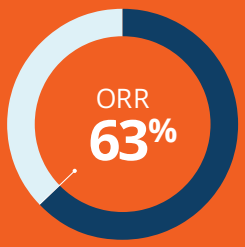
Gamifant is the first and only approved treatment for primary HLH[6,7]

In clinical studies, Gamifant was shown to be effective treatment for primary HLH in patients with refractory, recurrent, or progressive disease or who were intolerant of conventional treatment.[6]

- Multicenter, open-label, single-arm study of pharmacokinetics, efficacy, and safety of Gamifant in patients with suspected or confirmed primary HLH who had refractory, recurrent, or progressive disease during conventional HLH therapy or were intolerant to it[6]
  - **SAFETY** was evaluated in **34 patients**, 7 of whom were treatment naïve
  - **EFFICACY** was evaluated solely in **27 pediatric patients** who had already received conventional HLH treatment
- Patients had received a median of 3 prior agents as part of standard care before enrollment into the trial; prior regimens included combinations of dexamethasone, etoposide, cyclosporine A, and anti-thymocyte globulin[6]
- Median age of patients in the study was 1 year (range: 0.1-13 years)[6]



Primary endpoint was overall response rate (ORR) at the end of treatment, defined as achievement of either complete or partial response or HLH improvement.[6]

- **In patients with unsatisfactory response to conventional treatments, Gamifant achieved 63% ORR (95% CI: 0.42, 0.81; *P* = 0.013)[6]**

Secondary endpoints included time to response, durability of response, steroid reduction by 50% or more of baseline dose, and patients proceeding to hematopoietic stem cell transplantation (HSCT) when indicated.[7]

- **70% of patients (19/27) proceeded to HSCT[6]**

Important Safety Information

Infections

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.

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.

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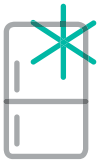
Supplies required for Gamifant preparation and infusion

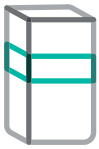
Gamifant is administered as an intravenous infusion over 1 hour twice a week (every 3 to 4 days) until HSCT is performed. You will need the following supplies:

- Gamifant single-dose vials
- Gamma irradiated, latex-free, polyvinyl chloride (PVC)-free syringe (20 mL or larger syringe). Do not use with ethylene oxide-sterilized syringes
- Non-PVC polyolefin infusion bag (dependent on volume needed)
- 0.9% sodium chloride for injection, USP
- Intravenous line with sterile, non-pyrogenic, low-protein binding 0.2 µm in-line filter

Storage and handling



- Store in a refrigerator at 2°C to 8°C (36°F to 46°F). Gamifant contains no preservative



- Store in original carton to protect from light

- DO NOT FREEZE OR SHAKE

- Do not transport via pneumatic tube

How supplied

Gamifant Injection is supplied in the following packaging configurations:

- NDC 66658-501-01—containing one 10 mg/2 mL (5 mg/mL) single-dose vial
- NDC 66658-505-01—containing one 50 mg/10 mL (5 mg/mL) single-dose vial
- NDC 66658-510-01—containing one 100 mg/20 mL (5 mg/mL) single-dose vial

Not actual size.

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Premedication and concomitant medications

Premedication

- Administer prophylaxis for herpes zoster, *Pneumocystis jirovecii*, and for fungal infections prior to Gamifant® (emapalumab-lzsg) administration

Concomitant medications

- Gamifant should be given concomitantly with dexamethasone
- For patients who are not receiving baseline dexamethasone treatment, begin dexamethasone at a daily dose of at least 5 to 10 mg/m^2 the day before Gamifant treatment begins
- Patients who are receiving baseline dexamethasone may continue their regular dose provided the dose is at least 5 mg/m^2
- Dexamethasone can be tapered according to the judgment of the treating physician
- 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

Monitor patients for infusion-related reactions

Interrupt infusion for infusion-related reactions and institute appropriate medical management prior to continuing infusion at a slower rate

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Steps in preparing and administering Gamifant to patients

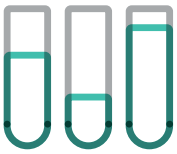
STEP 1 Calculate the Gamifant dose

There are four variables to any Gamifant dose infusion

- Patient weight in kg
- Desired mg/kg dose
- Desired total infusion volume (to be administered over 1 hour)
- Patient condition (restrict total infusion volume; see chart on page 9)

Record actual patient weight

The weight of the patient must be taken prior to preparation of Gamifant for administration, ideally on the same day as the infusion.



Select the patient dose in mg

(Can be 1 mg/kg, 3 mg/kg, 6 mg/kg, or 10 mg/kg) Patient weight (kg) x dose ([selected] mg/kg) = total mg of Gamifant needed.

Infusion-related reactions

- Mild to moderate infusion-related reactions, including drug eruption, pyrexia, rash, erythema, and hyperhidrosis, were reported with Gamifant in 27% of patients
- In one-third of these patients, the infusion-related reactions occurred during the first infusion
- No infusion-related reactions led to premature withdrawal or were reported as serious adverse events

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STEP 2 Calculate the total infusion volume and number of vials needed

Recommended infusion volumes based on dose, infusion concentration, and patient weight

Patient Weight (kg)		3	5	10	15	20	25	30	40	50	60	70	90
Dose	Gamifant concentration in infusion solution												
1 mg/kg	0.5 mg/mL	6	10										
1 mg/kg	1 mg/mL			10	15	20	25	30	40	50	60	70	90
3 mg/kg	1 mg/mL	9	15	30	45	60	75	90					
3 mg/kg	2 mg/mL								60	75	90	105	135
6 mg/kg	2 mg/mL	9	15	30	45	60	75	90					
6 mg/kg	2.5 mg/mL								96	120	144	168	216
10 mg/kg	2 mg/mL	15	25	50	75								
10 mg/kg	2.5 mg/mL					80	100	120	160	200	240	280	360

Total mg of Gamifant needed (from Step 1) ÷ selected mg/mL concentration = Total mL of Gamifant needed

Note: In cases where patient condition requires restriction of total infusion volume, higher concentration of infusion solution than those recommended can be used as long as the final concentration of infusion solution remains ≤ 2.5 mg/mL. Do not dilute product to < 0.25 mg/mL.

Calculate the number of vials needed per dose of Gamifant

Gamifant is available as 20 mL, 10 mL, or 2 mL vials

- Total mg of Gamifant needed ÷ 5 mg/mL Gamifant concentration
- Divide by 20 mL, 10 mL, or 2 mL for # of vials of Gamifant
- Vials are single-use only. Any remaining drug must be discarded

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Vial calculation example

If a patient weighs 5 kg and a 6 mg/kg dose is selected, then the total dose of Gamifant needed is 30 mg.

To calculate the number of vials needed for a 30 mg dose, divide by 5 mg/mL.

- 30 mg divided by 5 mg/mL = 6 mL of Gamifant
- 6 mL would require one 10 mL vial of Gamifant, which would produce 4 mL of waste. Or, select three 2 mL vials of Gamifant for exactly 6 mL of drug

STEP 3 Select the appropriate bags or syringes

Depending on the dose to be administered and the weight of the patient, the diluted sterile concentrate can be administered either in 20 mL or larger syringes or in a 0.9% sodium chloride for injection, USP infusion bag of the appropriate size, depending on the volume to be infused.

Note: Do not use with ethylene oxide-sterilized syringes

STEP 4 Prepare Gamifant dilution

Prepare the solution for infusion as follows:

- After removing from refrigerator, inspect Gamifant vials visually for particulate matter and discoloration prior to dilution. Gamifant is a clear to slightly opalescent, colorless to slightly yellow liquid. Do not administer if discolored or foreign particulate matter is present
- Withdraw the necessary amount of Gamifant solution and dilute with 0.9% Sodium Chloride Injection, USP to a maximum concentration of 2.5 mg/mL. Do not dilute product to less than 0.25 mg/mL
- Discard any unused portion left in the vial(s). Gamifant vials are for single use only
- The diluted solution can be placed in either a syringe or an infusion bag, depending on the volume needed

- Gently invert the infusion bag or syringe several times to ensure complete and homogeneous distribution of Gamifant

- DO NOT SHAKE

- Once the infusion solution is prepared, it should be clearly labeled for administration to the patient

Please see page 12 for more information on infusion concentration parameters

Storage of diluted solution

Gamifant vials do not contain a preservative. If not administered immediately:

- Store the diluted solution of Gamifant under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 4 hours from the time of dilution
- If refrigerated, allow the diluted solution to come to room temperature prior to administration
- Do not freeze or shake

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Parameters to consider for the preparation of Gamifant solution for infusion

An appropriate concentration of Gamifant in the infusion solution has to be chosen in order to optimize the final volume of the solution to be infused.

- The maximum volume of non-diluted drug (5 mg/mL) to be administered should not exceed 50% of the total volume of the final solution. Therefore the maximum concentration to be used should be 2.5 mg/mL
- The total volume to be administered should take into account pediatric infusion guidelines:
  - For patients weighing less than 10 kg, the maximum volume to be administered should be 4 mL/kg/hr
  - For patients weighing between 10 and 20 kg, the maximum volume to be administered should be 6 mL/kg/hr

The volume of the infusion solution to be prepared depends on priming or flushing.

- **Priming**

  The volume of the infusion line between the syringe and the intravenous catheter is taken into account in the final volume contained in the syringe or the bag.

- **Flushing**

  The volume in the syringe or bag must be entirely delivered, which means that the infusion line is gently flushed with saline once the infusion is completed. If flushing is part of the infusion process to deliver the full dose, it should be performed immediately after the end of the infusion.

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STEP 5 Administer Gamifant by IV infusion

Gamifant is administered as an intravenous infusion over 1 hour twice a week (every 3 to 4 days) until HSCT is performed or unacceptable toxicity.

Discontinue Gamifant when a patient no longer requires therapy for the treatment of HLH.

- Administer Gamifant diluted solution intravenously over 1 hour through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 µm in-line filter
    - The duration of the infusion should be adapted when the volume to be infused is above the usual pediatric infusion recommendations (see table on page 9)

- Do not store any unused portion of the infusion solution for reuse. Any unused product or waste material should be disposed of in accordance with local requirements

Please remember that infusion-related reactions can occur, including during the first infusion. Monitor patients for infusion-related reactions. Interrupt infusion for infusion reactions and institute appropriate medical management prior to continuing infusion at a slower rate.

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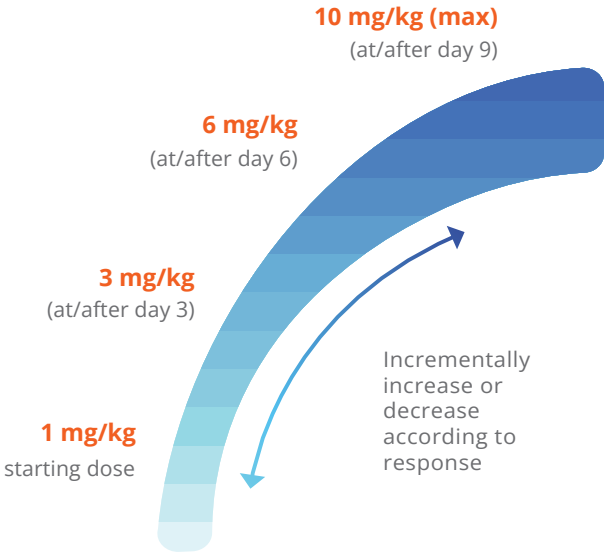
Gamifant dosing can be modified according to patient response



Gamifant offers flexibility of dosing and can be incrementally titrated upward or downward according to the clinician's assessment of patient response.

After the patient's clinical condition is stabilized, decrease the dose to the previous level to maintain clinical response until HSCT.

Dexamethasone can also be tapered according to the judgment of the treating physician. See full Prescribing Information for Gamifant and page 7 for more details.

Dose increases should be based on both clinician assessment of unsatisfactory improvement in clinical condition, AND at least one of the following:

Platelet count	If baseline < 50,000/mm^3 and no improvement to > 50,000/mm^3
	If baseline > 50,000/mm^3 and less than 30% improvement
	If baseline > 100,000/mm^3, any decrease to < 100,000/mm^3
Fever	Persistence or recurrence
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 (mg/dL): if baseline levels ≤ 100 mg/dL and no improvement or if baseline levels > 100 mg/dL and any decrease to < 100 mg/dL

Effect of Gamifant on CYP450 substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (such as IFNγ) during chronic inflammation. By neutralizing IFNγ, use of Gamifant may normalize CYP450 activities which may reduce the efficacy of drugs that are CYP450 substrates due to increased metabolism. Upon initiation or discontinuation of concomitant Gamifant, monitor for reduced efficacy and adjust dosage of CYP450 substrate drugs as appropriate.

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gamifant cares™
Support for the journey ahead

Access and reimbursement support

Gamifant Cares

The first step to access is completing the Prescription and Enrollment Form

By completing and submitting the form to Gamifant Cares your patient will be enrolled. Gamifant Cares will perform a benefit investigation and send you a summary of benefits. Additionally, Gamifant Cares will identify potential financial assistance options that may be available to help eligible patients with financial needs.

Simply download and complete the Gamifant Enrollment Form found at Gamifant.com and fax it to Gamifant Cares at **866.895.7204**.

- Be sure to include copies of your patient's insurance and pharmacy benefit cards
- Double-check that all required fields have been completed so as not to delay access

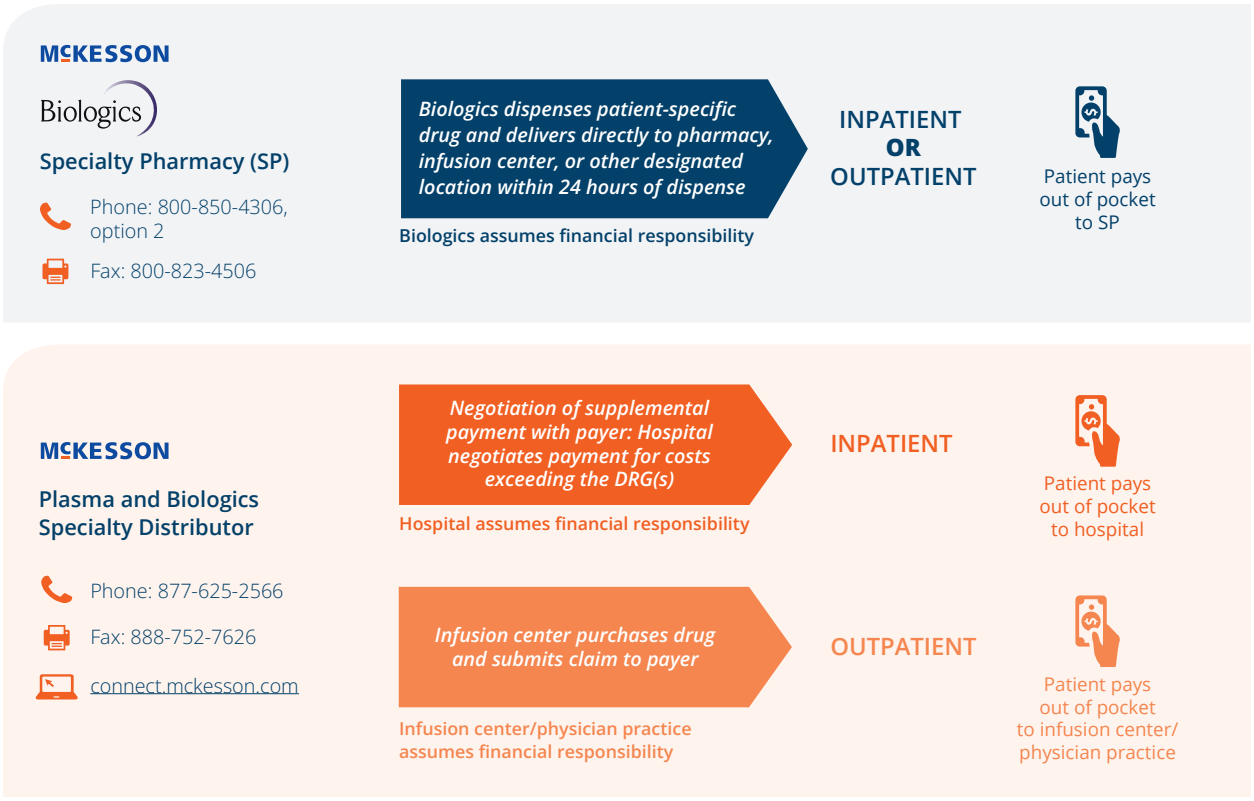
Gamifant Cares will send you an acknowledgment after receiving the Prescription and Enrollment Form for your patient. After completing the benefit investigation Gamifant Cares will send you a summary of benefits and follow up with a phone call to answer any questions you may have.

Questions? We are here to help.

833.597.6530

Ordering Gamifant

There are **2 pathways to access Gamifant**. Keep in mind that your institution and the patient's insurance will dictate how Gamifant should be ordered.



DRG=diagnosis-related group.

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Gamifant Cares

Gamifant Cares offers personalized support and resources to help patients and their families throughout treatment with Gamifant. Gamifant Cares provides information regarding patient healthcare coverage options and financial assistance information that may be available to help patients with financial needs. Gamifant Cares can:

- Evaluate a patient's insurance coverage and help with navigating and understanding the insurance process
- Provide financial assistance information
- Identify potential financial assistance options that may be available to help eligible patients with financial needs

To learn more, contact us at 833.597.6530.

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For more information, please visit:

Gamifant.com

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