Drug Use Research & Management Program
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New Drug Evaluation: emapalumab-lzsg, injection

Date of Review: June 2020
Generic Name: emapalumab-lzsg

End Date of Literature Search: 10/09/19
Brand Name (Manufacturer): Gamifant (Novimmune SA)

Dossier Received: yes

Research Questions:

1. What is the efficacy of emapalumab for the treatment of primary hemophagocytic lymphohistiocytosis (pHLH) with refractory, recurrent or progressive disease or intolerance to conventional HLH therapy?
2. Is emapalumab safe for the treatment of pHLH?
3. Are there subgroups of patients with pHLH for which emapalumab is more effective or associated with fewer adverse events?

Conclusions:

- There is insufficient evidence from one unpublished, non-randomized open-label trial that emapalumab treatment resulted in a statistically significant overall response rate compared to placebo in pHLH patients intolerant or refractory to conventional therapy [63% (95% CI: 0.42 to 0.81; p=0.0134)].[1]
- Low quality evidence for safety of emapalumab over 8 weeks suggests risk for infections (56%), hypertension (41%), infusion-related reactions (27%), and pyrexia (24%).[1,2]
- There is insufficient evidence to evaluate the efficacy and safety of emapalumab beyond 8 weeks and to assess long-term clinical outcomes. [1,2]

Recommendations:

- Create Preferred Drug List (PDL) class for Drugs for hemophagocytic lymphohistiocytosis (HLH).
- Designate emapalumab-lzsg as non-preferred.
- Implement clinical prior authorization for emapalumab to ensure appropriate utilization (**Appendix 2**)

Background:

Hemophagocytic lymphohistiocytosis (HLH) is a rare and fatal syndrome of hyperinflammation, tissue damage, and multi-organ failure.[3] HLH is caused by defective cytotoxic T lymphocyte (CTL) and natural killer (NK) cell communication pathways which leads to excessive cytokine production, unregulated immune cell activation, and destructive macrophage accumulation in tissues and organs.[3] The abnormal immune response observed in HLH may originate from a primary genetic defect or be acquired secondary to an environmental trigger.[4] HLH typically manifests in infants and younger children up to 18 months; however, the disease may also present in adults and the elderly.[5] HLH patients commonly present with a high fever, cytopenia, coagulopathy, and hepatosplenomegaly with

lymphadenopathy. Up to 65% of pediatric HLH patients display a nonspecific macropapular rash as well.[6] Approximately 25-50% of primary HLH patients experience neurologic problems which range from headaches and irritability to encephalopathy, seizures, and coma.[7] As HLH progresses, patients exhibit further hepatic decline and neurologic complications with eventual multi-organ dysfunction and death.[7] If untreated, studies have shown patients with primary HLH (pHLH) have a median survival of roughly 2 months.[8] Therefore, most pHLH patients will eventually require allogeneic hematopoietic stem cell transplantation (HSCT) which improves 3-year survival rate from almost 0% to 50%. [3,9] The mortality rate for secondary acquired HLH is above 50%.[8] The overall incidence of HLH is estimated to be 12 per million worldwide and a prevalence of roughly 1 in 100,000 in the United States.[10,11] Within the past year, there were approximately 14 Oregon Medicaid patients with HLH-related claims and 3 were in the Fee-for-Service (FFS) program.

In normal immune function, cytotoxic T lymphocytes (CTLs), natural killer (NK), and T-regulatory cells control infection and inflammation through granule-mediated cytotoxicity.[12] Macrophages present foreign antigens to lymphocytes for direct termination and help stimulate the development of antibodies.[13] In HLH, there are defects in the signaling pathways and feedback loops that govern typical immune response.[13] With the inflammatory cascade left unchecked, lymphocytes and macrophages continue to proliferate and secrete high levels of pro-inflammatory cytokines such as interferon gamma, tumor necrosis factor-alpha, macrophage colony-stimulating factor, and several interleukins.[14] IFN-gamma is alleged to play a crucial role in macrophage hemophagocytosis while elevated TNF levels have been associated with increased hypofibrinogenemia and other blood dyscrasias.[15,16] The hyperactivated macrophages, NK cells, and CTLs, along with cytokine storm, is believed to be the origin of tissue damage and destruction.[13]

HLH is a heterogeneous spectrum of clinically similar subtypes, so it is often difficult for clinicians to differentiate from other infections, hematological malignancies, and cytokine storm syndromes.[3,17] When HLH presents in neonates, it may be overlooked and mistakenly treated as sepsis.[3,18] Children with an exaggerated response to infections along with extremely high cytokine levels and low/absent NK cell function are suspected to have HLH.[3] To facilitate a more rapid and specific diagnosis, the Histiocyte Society updated guidelines in 2004 to standardize HLH criteria.[19] A positive HLH diagnosis requires that 5 of 8 criteria be met (see **Table 1)** unless HLH is confirmed through genetic tests.[19] The diagnostic guidelines are mostly based on clinical experience with children but are commonly applied to all suspected HLH patients. [9]

Table 1: Hemophagocytic Lymphohistiocytosis Diagnostic Criteria [19]

HLH diagnosis fulfilled if patients meet 5 out of 8 criteria listed below:
Fever
Hemophagocytosis in bone marrow or spleen or lymph nodes
Low or absent NK-cell activity (according to local laboratory reference)
Ferritin ≥500 µg/L
Soluble CD25 (i.e. soluble IL-2 receptor) ≥2,400 U/mL
Splenomegaly
Hypertriglyceridemia and/or hypofibrinogenemia: Fasting triglycerides ≥3.0 mmol/L (≥265 mg/dL) or Fibrinogen ≤1.5 g/L
Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood): Hemoglobin <90 g/L (in infants <4 weeks: hemoglobin <100g/L); Platelets <100 x 109/L; Neutrophils <1.0 x 109/L

Primary HLH (pHLH) is often connected with family history and/or a homozygous mutation.[9] Reactive, or secondary HLH (sHLH) is mostly acquired via immune activation usually provoked by infection, malignancy, metabolic conditions, or an underlying autoimmune/rheumatologic disorder.[9,17] Primary HLH may be further subclassified into familial lymphohistiocytosis (FHL) which is usually an autosomal recessive genetic mutation of one of 4 genes in the lymphocyte perforin pathway.[9] Primary HLH may also be associated with other immune function diseases.[17,20] Classification of various HLH subtypes are listed in **Table 2**. Secondary HLH is generally associated with underlying conditions such as severe infections, malignancies, or inflammatory disease.[4,20] Although pHLH has historically been exclusively associated with genetic mutation, recent evidence indicates the possibility of genetic predisposition in secondary HLH as well.[21] Knowledge of the patient's genetic factors may help predict the chance of recurrence, need for HSCT, and future risk of HLH for family members. [4,9,20]

Table 2. Classification of Primary and Secondary HLH [9]

Classification	Subtype/Association	Etiology
Primary HLH	Familial HLH type 1	Unknown gene mutation
	Familial HLH type 2	PRF1 gene mutation
	Familial HLH type 3	UNC13D gene mutation
	Familial HLH type 4	STX11 gene mutation
	Familial HLH type 5	STXBP2 gene mutation
	Griscelli syndrome type 2	RAB27A gene mutation
	Chediak–Higashi syndrome	LYST gene mutation
	Hermansky–Pudlak syndrome type 2	AP3B1 gene mutation
	X-linked lymphoproliferative disease – Type 1	SH2D1A gene mutation
	X-linked lymphoproliferative disease – Type 2	XIAP gene mutation
Secondary HLH	Infection	Viral (EBV, CMV, etc.)
		Bacterial (*Mycobacterium*, etc.)
		Fungal (*Histoplasma*, etc.)
		Parasitic (*Leishmania*, etc.)
	Malignancy	Lymphoma, leukemia, etc.
	Autoimmune/Inflammatory diseases "Macrophage activation syndrome"	sJIA, SLE, Kawasaki disease, etc.

Abbreviations: CMV = cytomegalovirus; EBV = Epstein-Barr virus; HLH = Hemophagocytic lymphohistiocytosis; SLE = systemic lupus erythematosus; sJIA = systemic juvenile idiopathic arthritis

Current treatment for HLH involves a multi-faceted approach with the inclusion of both immediate and long-term strategies.[22] Therapy options include immunosuppressants, immunomodulators, biologic response modifiers, treatment of underlying illness (if acquired HLH), and HSCT.[19,22] Ascertainment of disease etiology assists in the treatment plan, although in most cases, primary and secondary HLH generally follow the same initial protocol at the time of diagnosis.[3] The overarching goal is to suppress hyperinflammation and immune system dysfunction that decimates organs and leaves the patient vulnerable to deadly infections.[23] Infected macrophages must also be destroyed in order to halt the unregulated inflammatory cascade.[3] If pHLH has been confirmed, patients typically undergo 8 weeks induction phase of chemotherapy and immunotherapy to achieve remission followed by a continuation phase until HSCT.[4] Primary HLH patients unable to receive HSCT routinely yield to infections, bleeding, and/or multi-organ dysfunction and require intensive care and support due to

complications.[3] For acquired (secondary) HLH, identification and immediate treatment of the underlying infection, malignancy, or autoimmune disease is priority. [24]

Although there are no high-quality clinical guidelines for the treatment of HLH, in 1994, the Histiocyte Society presented a set of diagnostic and treatment protocols to assist in HLH management.[25] The protocol was updated in 2004 with minor changes; however, the agents and principles behind treatment have remained largely unchanged up to the present time.[19,22] In general, core HLH therapy has consisted of a combination of etoposide and dexamethasone at body surface area (BSA)-based doses administered at routine intervals in preparation for HSCT.[14] It has been demonstrated that the HLH-94 protocol has enabled over 71% of pHLH patients to survive to HSCT.[23] Etoposide is believed to induce activated T-cell death and suppress cytokine production while dexamethasone serves as important anti-inflammatory corticosteroid due to its long half-life and ability to concentrate in the cerebrospinal fluid.[26,27] Cyclosporine has often been incorporated into the 8-week induction regimen, but the timing and utility differs with respect to whether the HLH-94 or HLH-2004 protocol is used.[4] Immune globulins such as intravenous immunoglobulin have also shown some benefit in HLH treatment.[28] Direct evidence is limited for other immune-modulators and/or biological response modifiers such as rituximab, etanercept, infliximab, and alemtuzumab although some small observational studies have reported benefit.[22,29,30] **Table 3** is a summary of standard HLH therapy that have been used in large, multicenter trials sponsored by the Histiocyte Society.[1,19] It has been suggested that all primary genetic HLH patients and many secondary cases be treated with HSCT to improve outcomes.[31,32] Many studies have demonstrated HSCT to effectively control and possibly cure the disease altogether.[31,32]

Table 3. Standard First-Line Therapy for Hemophagocytic Lymphohistiocytosis (HLH)[1,19]

Regimen	Population	Dosing/Administration	Efficacy Information	Important Safety and Tolerability Issues
HLH-2004 N=369 N=168 with family history or genetically verified HLH	Previously untreated pediatric patients with pHLH	Initial: -Etoposide 150 mg/m^2 twice per week for 2 weeks then weekly for 6 weeks; -Dexamethasone 10 mg/m^2/daily tapered every 2 weeks until week 8 Continuation until HSCT: -Dexamethasone pulses 10 mg/m^2 every 3 days every second week -Etoposide infusions 150 mg/m^2 every alternating second week -Cyclosporine orally daily (goal trough level: 200 mcg/L) -Methotrexate IT at a maximum of 4 doses only during weeks 3–6 if neurological symptoms progress during the first 2 weeks or if abnormal CSF at onset has not improved after 2 weeks -CSF analysis and brain MRI should be performed at new onset or reactivation of neurological symptoms	Response rates: not reported Survival to transplant: 81% OS (5-year): 61% (95% CI: 56% to 67%)	Addition of cyclosporine upfront did not improve outcomes – no longer recommended during induction

Abbreviations: CI=confidence interval; CSF=cerebrospinal fluid; HLH=hemophagocytic lymphohistiocytosis; HSCT= hematopoietic stem cell transplantation; IT= intrathecal; IV=intravenous; MRI = magnetic resonance imaging; OS=overall survival

Clinical Efficacy:
Emapalumab (Gamifant®) is a monoclonal antibody for the treatment of pHLH.[1,2] Emapalumab binds to the interferon gamma (IFNγ) receptor to neutralize free and receptor-bound IFNγ.[1,2] The agent was designated a Breakthrough Therapy by the FDA and given priority review status in March of 2016. The drug was approved for the treatment of adult and pediatric pHLH in November 2018.[1] There are no other FDA-approved drugs for refractory, recurrent, or progressive pHLH or for those who are intolerant to conventional pHLH therapy.[1] Emapalumab is initially dosed at 1 mg/kg administered intravenously over 60 minutes twice weekly, titrated to 3, 6, or 10 mg/kg based on clinical response and laboratory parameters, then continued until HSCT or unacceptable toxicity.[1,2] Pharmacokinetic data demonstrated no need to adjust dose based on patient age, race, gender, renal or hepatic impairment.[1,2] See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, and use in specific populations.

There are currently no published studies available to evaluate the efficacy and safety of emapalumab, and therefore the risk of bias and financial disclosures could not be assessed. FDA Center for Drug Evaluation and Research review provided evidence for the efficacy summary. Given the rarity of pHLH, challenges in diagnosis and assessment, and the severity of clinical symptoms, the FDA reviewers determined that an adequately powered randomized controlled trial would be unfeasible.[1] Therefore, one 8-week, phase 2/3, multi-center, single-arm, non-randomized, open-label clinical trial was used for approval.[1] The study enrolled 34 patients: 27 had recurrent pHLH or refractory to standard treatment (second-line patients) and 7 were considered treatment naive (de novo) as determined by the physician.[1,2] Median age of subjects was 1 year, 53% were female, and 65% identified as White, 11% Asian, and 11% Black.[1,2] One-quarter of the subjects were from the United States.[1,2] The HLH diagnosis was based on genetic confirmation or fulfillment criteria as outlined by the Histiocyte Society (see **Table 1**).[1] Eighty-two percent of the patients had a genetic mutation recognized to cause HLH.[1] Patients with a diagnosis of secondary HLH consequent to a rheumatic or neoplastic disease were excluded as were those with active bacterial infections, malignancy, concomitant cardiovascular, pulmonary, liver, or renal disease.[1]

Emapalumab was administered as an intravenous infusion at 1 mg/kg every 3 to 4 days and was adjusted up to 10 mg/kg based on clinical response.[1,2] Almost half (44%) of the patients remained on the starting dose and the rest required a dose escalation.[1] All patients received concomitant dexamethasone therapy throughout the study.[1,2] Follow-up was for 1 year after transplant or last emapalumab dose.[1] The primary efficacy endpoint was overall response rate, defined as achievement of complete or partial response or HLH improvement at end of 8-week treatment or until HSCT if clinically warranted between 4 and 8 weeks.[1,2] See **Table 4** for summary of response rate definitions. The secondary outcomes included duration of response, percent of patients with steroid reduction, percent of patients proceeding to HSCT, and overall survival pre-and post-transplant.[1] Secondary outcomes were considered supportive and did not undergo formal statistical tests.[1]

Table 4: Overall Response Rate Definitions[1]

Overall Response Rate	
Complete Response	No fever (body temperature <37.5 ˚C)
	Normal spleen size as measured by 3D abdominal ultrasound
	No cytopenia
	No hyperferritinemia
	No evidence of coagulopathy
	No neurological and CSF abnormalities attributed to HLH
	No sustained worsening of soluble interleukin-2 receptor (sCD25)

Partial Response	≥3 of the HLH clinical and laboratory abnormalities (including CNS abnormalities) met the aforementioned criteria for "complete response"
	In "reactivated patients" who entered the study with 3 abnormal HLH features, ≥2 criteria needed to meet the definition given
	There was no progression of other aspects of HLH disease pathology (e.g., jaundice, edema, CNS effects)
HLH improvement	Improvement (>50% change from baseline) of ≥3 HLH clinical and laboratory abnormalities (including CNS involvement)
	In "reactivated patients" who entered the study with 2 abnormal HLH features, a change from baseline greater than 50% for both defined HLH as improved

Abbreviations: CNS = central nervous system; CSF = cerebral spinal fluid; HLH = hemophagocytic lymphohistiocytosis

Thirty-four pHLH patients were treated with emapalumab, but FDA approval was based on efficacy results in only second-line patients intolerant or refractory to conventional therapy (n=27).[1] Of these 27 participants, 20 (74%) completed the study and the rest died.[1,2] The reported overall response rate was 63% (95% CI: 0.42 to 0.81; p=0.0134) with complete response reached by 26% of patients, partial response achieved by 30%, and HLH improvement achieved by 7%.[1,2] Nineteen of 27 (70%) patients proceeded to HSCT.[1]

There were limitations as to what conclusions could be drawn for emapalumab efficacy based on the data provided. The criteria to meet the definition of a patient with refractory, recurrent, or progressive pHLH was not specified but individually determined by the treating physician. In addition, the study outcome measures only applied to second-line treatment populations so the effects of emapalumab on treatment-naïve patients is unclear. Larger patient cohorts and more data are needed to determine the role of emapalumab in previously untreated patients. The data were insufficient to statistically evaluate secondary outcomes of response duration and overall survival. Although the investigators assessed time-to event endpoints with a Kaplan-Meier analysis, the reviewers were unable to interpret the findings due to the single arm trial design.

Clinical Safety:

The FDA clinical review analyzed safety data for all patients who had received emapalumab in the controlled study (n=34).[1] A total of 10 of the 34 treated patients died. In the primary efficacy cohort, 7 of the 27 (26%) patients died and six of those deaths occurred while in active treatment with emapalumab. Over half of the deaths were in patients who had developed a new infection or a deterioration of a pre-existing infection. Two fatalities (6%) were due to gastrointestinal hemorrhage and septic shock.[1] Other adverse effects associated with emapalumab during clinical trials included hypertension, infusion-related reactions, and pyrexia.[1,2] Incidence of adverse effects that occurred more frequently than 10% are outlined in **Table 5**.[1,2] The serious adverse events (SAEs) reported in 53% of patients were most commonly related to infections (32%), gastrointestinal hemorrhage (9%), and multiple organ dysfunction (6%).[1,2] Serious infections included sepsis, pneumonia, bacteremia, disseminated histoplasmosis, necrotizing fasciitis, and perforated appendicitis.[1] There were 9 patients (27%) that reported infusion-related reactions within 24 hours of emapalumab administration, but none were graded as severe and none led to discontinuations.[1] Due to the infection risk, manufacturer labeling recommends that patients be monitored for tuberculosis (TB), adenovirus, cytomegalovirus (CMV), and Epstein-Barr virus (EBV) every 2-weeks and as clinically indicated.[2]

Table 5. Adverse Reactions Reported in ≥ 10% of Patients with Primary HLH[1,2]

Adverse Reactions	GAMIFANT (%) (N = 34)
Infections [a]	56
Hypertension [b]	41
Infusion-related reactions [c]	27
Pyrexia	24
Hypokalemia	15
Constipation	15
Rash	12
Abdominal pain	12
Cytomegalovirus infection	12
Diarrhea	12
Lymphocytosis	12
Cough	12
Irritability	12
Tachycardia	12
Tachypnea	12

[a]Includes viral (30%), bacterial (15%), fungal (15%), and infections in which no pathogen was identified
[b]Includes secondary hypertension
[c]Includes events of drug eruption, pyrexia, rash, erythema, and hyperhidrosis

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Quality of life
2) Improved function
3) Survival
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Overall response rate
2) HLH improvement

Table 6. Pharmacology and Pharmacokinetic Properties.[1,2]

Parameter	
Mechanism of Action	Monoclonal antibody that binds to and neutralizes interferon gamma which is hypersecreted in HLH
Oral Bioavailability	N/A
Distribution and Protein Binding	4.2 L central; 5.6 L peripheral. Protein binding not evaluated (not expected to bind to plasma proteins).
Elimination	0.007 Liters/hour
Half-Life	22 days in healthy subjects; 2.5 to 18.9 days in HLH patients
Metabolism	Degraded into small peptides and amino acids via catabolic pathways

Abbreviations: HLH=hemophagocytic lymphohistiocytosis

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GAMIFANT safely and effectively. See full prescribing information for GAMIFANT.

GAMIFANT™ (emapalumab-lzsg) injection, for intravenous use
Initial U.S. Approval: 2018

INDICATIONS AND USAGE

GAMIFANT 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. (1)

DOSAGE AND ADMINISTRATION

For intravenous infusion only:

- Recommended starting dosage: 1 mg/kg as an intravenous infusion over 1 hour twice per week. (2.1)
- Administer dexamethasone concomitantly with GAMIFANT. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection:

- 10 mg/2 mL (5 mg/mL) solution in a single-dose vial (3)
- 50 mg/10 mL (5 mg/mL) solution in a single-dose vial (3)

CONTRAINDICATIONS

- None. (4)

WARNINGS AND PRECAUTIONS

- Infections: Monitor patients for signs and symptoms and treat promptly. Test for latent tuberculosis. Administer prophylactic treatment against Herpes Zoster, *Pneumocystis jirovecii* and fungal infections. (5.1)
- Live Vaccines: Do not administer live or live attenuated vaccines to patients receiving GAMIFANT. (5.2)
- Infusion-Related Reactions: Monitor patients for infusion-related reactions. Interrupt infusion for severe infusion reactions and institute appropriate medical management. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (≥ 20%) were: infections, hypertension, infusion-related reactions, and pyrexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact 1-866-773-5274 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2018

Emapalumab

Goal(s):
- To ensure appropriate use of emapalumab in patients with primary hemophagocytic lymphohistiocytosis (pHLH).

Length of Authorization:
- 2 - 6 months

Requires PA:
- Emapalumab

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1: Diagnostic Criteria for pHLH

≥ 5 of the following 8 criteria at baseline	Fever
	Splenomegaly
	Cytopenias (2 or more): - Hemoglobin <9 g/dL (infants <4 weeks: <10 g/dL) - Platelets <100 x 109/L - Neutrophils <1 x 109/L
	Hypertriglyceridemia (fasting, >265 mg/dL) or hypofibrinogenemia (<150 mg/dL)
	Hemophagocytosis in spleen, bone marrow, lymph nodes or liver
	Low or absent NK cell activity
	Ferritin >500 µg/L
	Elevated soluble CD25 (interleukin 2 receptor alpha) ≥2,400 units/mL
OR	
Molecular Genetic Testing	Biallelic pathogenic gene variant (eg. *PRF1, UNC13D, STX11, or STXBP2*) or family history consistent with primary HLH

Table 2: Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Primary HLH	1 mg/kg IV twice per week (every 3 to 4 days)	10 mg/kg/dose

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes**: Go to **Renewal Criteria**	**No**: Go to #2
2. What diagnosis is being treated?	Record ICD10 code.	
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this agent being prescribed for treatment of refractory, recurrent, or progressive primary HLH or for those who are intolerant to conventional primary HLH therapy? *Conventional therapy should have included an etoposide and dexamethasone-based regimen*	**Yes:** Document prior therapies or reasons for failure. Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Has the diagnosis of pHLH been confirmed by genetic testing or by diagnostic criteria listed in **Table 1**?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the agent prescribed by or in consultation with a specialist (e.g. hematologist) with experience in treating HLH patients?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is the agent being prescribed concurrently with dexamethasone?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
8. Is there documentation that the prescriber has assessed the patient and found no evidence of active infection?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
9. Has the patient received prophylaxis for Herpes Zoster, *Pneumocystis Jirovecii*, and fungal infections?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
10. Is there documentation that the patient has been evaluated and will continue to be monitored for TB, adenovirus, EBV, and CMV every 2 weeks as clinically appropriate?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness.
11. Is the agent dosed appropriately based on documentation of a recent patient weight (see **Table 2** above)?	**Yes:** Document patient weight and go to #12 Weight:_____	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is there attestation that the patient and provider will comply with case management to promote the best possible outcome for the patient and adhere to monitoring requirements required by the Oregon Health Authority?	**Yes:** Approve for 2 months.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Does the patient show evidence of developing any serious infections, severe infusion reactions, or unacceptable toxicity related to emapalumab treatment/administration?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No**: Go to #2
2. Is emapalumab being prescribed concurrently with dexamethasone?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the patient receiving ongoing monitoring for TB, adenovirus, EBV, and CMV every 2 weeks as clinically appropriate?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the provider attest that the patient has not yet received hematopoietic stem cell transplantation (HSCT)?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
5. Has the patient's condition stabilized or improved as assessed by the prescribing provider?	**Yes**: Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 6/20 (DE)
Implementation: 9/1/2020