

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
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Review Completion Date	October 31, 2018
Subject	Evaluation of Need for a REMS
Established Name	Emapalumab-lzsg
Trade Name	Gamifant
Name of Applicant	Novimmune
Therapeutic Class	An interferon gamma blocking antibody
Formulation(s)	10 mg/2 ml and 50 mg/10 ml single-use vials
Dosing Regimen	1 mg/kg intravenous infusion twice per week. Doses may be increased based on clinical and laboratory criteria

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Gamifant (emapalumab-lzsg) is necessary to ensure the benefits outweigh its risks. Novimmune submitted a Biologic Licensing Application (BLA) 761107 for emapalumab with the proposed indication for 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. Untreated patients with HLH may have a survival of months. Even with treatment, only 21-26% are expected to survive 5 years. The risks associated with emapalumab-lzsg include serious and fatal infections, increased risk of infection with use of live vaccines, and infusion related reactions. The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Hematology Products (DHP) agree that a REMS is not needed to ensure the benefits of emapalumab outweigh its risks. The most concerning risk associated with emapalumab-lzsg is it may increase serious and fatal infections due to mycobacteria, herpes zoster, *hisoplasma capsulatum*, *Pneumocystis jirovecii*, and fungi. In general, patients with HLH are at greater risk for infections.¹ In the clinical trial, serious infections such as sepsis, pneumonia, bacteremia, disseminated histoplasmosis, necrotizing fasciitis, viral infections, were reported in 32% of patients. These risks will be communicated in the prescribing information warnings and precautions section if emapalumab-lzsg is approved. In addition, the prescribing information contains instructions to prescribers regarding the need for prophylaxis against herpes zoster, *Pneumocystis jirovecii*, fungal infection, and tuberculosis (if the patient is at risk for tuberculosis), as well as close monitoring, and initiation of appropriate antimicrobial therapy in the event of an infection. Other adverse events, such as an increased risk of infection with use of live vaccines, as well as infusion-related reactions will be described in the warnings and precautions section of the labeling. Additionally, if approved, the product labeling will contain a Medication Guide.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Gamifant (emapalumab-lzsg) is necessary to ensure the benefits outweigh its risks. Novimmune submitted a Biologic Licensing Application (BLA) 761107 for emapalumab-lzsg with the proposed indication for 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. This application is under review in DHP. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Emapalumab-lzsg, a NME, is an interferon gamma (IFN γ) blocking antibody proposed for treatment of adult and pediatric (newborn and older) patients with primary HLH with refractory, recurrent or

progressive disease or intolerance with conventional HLH therapy. Emapalumab-lzsg binds to and neutralizes the effects of IFN γ . Nonclinical data suggest that IFN γ plays a pivotal role in the pathogenesis of HLH by being hypersecreted, which results downstream effects of hypercytokinemia and inflammation. The plasma concentrations of Chemokine (C-X-C motif) ligand 9 (CXCL9), a chemokine induced by IFN γ , is reduced by Emapalumab-lzsg due to its actions to neutralize IFN γ . The pharmacokinetics (PK) and pharmacodynamics (PD) of emapalumab-lzsg are influenced by the level of IFN γ , which can vary between patients and within patients as a function of time. Due to the variability of the IFN γ production and the variability in the PK and PK/PD, the emapalumab-lzsg dose should be modified during treatment based on the monitoring of the patient's clinical and laboratory parameter.

Emapalumab-lzsg is produced by recombinant DNA technology in Chinese Hamster ovary cells. Emapalumab-lzsg proposed as 10 mg and 50 mg single-use vials to be given by intravenous route. The recommended dose is 1 mg/kg twice per week until hematopoietic stem cell transplantation (HSCT) is performed or until unacceptable toxicity. The dose may be increased based on clinical and laboratory parameters from 1 mg/kg to 3 mg/kg, then to 6 mg/kg and up to 10 mg/kg. Emapalumab-lzsg should be given concomitantly with dexamethasone. Emapalumab-lzsg is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761107 relevant to this review:

- March 26, 2010: orphan drug designation granted
- March 11, 2016: breakthrough designation granted
- August 25, 2017: rare pediatric drug designation granted
- March 20, 2018: BLA 761107 submission received
- July 5, 2018: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that "At this time a need for a REMS has not been identified".

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of excessive immune activation which is aggressive and life-threatening. Infants from birth to 18 months of age are most frequently affected by HLH, but is also observed in children and adults of all ages. Symptoms may include fever, enlarged liver or spleen, cytopenia, hyperferritinemia, coagulation defects, and neurological abnormalities (irritability, fatigue, abnormal muscle tone, seizures, neck stiffness, mental status changes, ataxia, blindness, paralysis, and/or coma).² HLH can occur as a familial or sporadic disorder, and it can be triggered by a variety of events that disrupt immune homeostasis. A common trigger of HLH is infection, both in those with a genetic predisposition and in sporadic cases.

Due to progressive multi-organ failure, untreated patients with HLH may have a survival of months^a. Those with an inherited mutation of HLH gene have a survival of about 2 months without treatment. In a series of 162 adults with HLH, 94 (58%) patients survived. Of the patients who did not survive, about half died within one month of diagnosis, especially those with hematologic malignancies.³ Even with treatment, only 21-26% are expected to survive 5 years. A study of 122 patients from the International Registry for HLH found that overall estimated 5-year survival rate was 21%, with 66% of patients who received bone marrow transplantation surviving 5 years versus only 10% of patients treated with chemotherapy alone.⁴

The incidence of HLH is reported to be 1.2 cases per million persons per year. However, because of improved detection, unpublished observations estimate that the figures have slightly increased over time, it may increase to 1 case per every 50,000 births.^b HLH has not been epidemiologically shown to have a preference of any race. A sample of European countries, including Sweden, England, and Italy, has reported similar statistical incidence.⁵

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

To suppress life-threatening inflammation by destroying immune cells is the goal of the therapy for patients with HLH. HLH-94 is the first treatment protocol for HLH organized by the Histiocyte Society in 1994. Induction therapy based on the HLH-94 consists of a series of weekly treatment with dexamethasone and etoposide (VP-16), with the addition of cyclosporine at week 9. Patients with central nervous system (CNS) disease are given intrathecal methotrexate. After induction, patients who are recovering are weaned off therapy, while those who are not improving are continued on therapy as a bridge to allogeneic hematopoietic cell transplantation (HCT). HCT will be required in those with an HLH gene mutation, CNS disease, or disease relapse.⁶

In 2004, a new HLH protocol was initiated (HLH-2004). The major modifications were to use cyclosporine earlier (ie, during the induction phase of therapy), and to add hydrocortisone to the intrathecal methotrexate. Until the results of HLH-2004 trial are available, the ideal therapy for patients with HLH remains unknown. Clinicians are encouraged to enter patients in clinical trials.

4 Benefit Assessment⁷

Study NI-0501-04 (NCT01818492) evaluated the efficacy of emapalumab-lzsg. This was 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. The inclusion criteria for enrollment were - primary HLH based

^a Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

^b Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

on a molecular diagnosis or family history consistent with primary HLH or five out of the eight criteria (hemoglobin <9, platelets <100 x 10⁹/L, neutrophils <1 x 10⁹/L, hypertriglyceridemia (fasting triglyceride >3 mmol/L or ≥265 mg/dL) and/or hypofibrinogenemia (≤1.5 g/L), hemophagocytosis in bone marrow, spleen, or lymph nodes with no evidence of malignancy, low or absent Nature Killer (NK) cell activity, ferritin ≥500 mcg/L, soluble CD25 ≥2400 U/mL. Patients with active infections were excluded from the trial.

Twenty-seven patients enrolled and received treatment in the study and 20 patients (74%) completed the study. Seven patients (26%) were prematurely withdrawn. Twenty-two patients (81%) enrolled onto the open-label extension study – NI-0501-05 (NCT 02069899) which monitored patients for up to 1 year after HSCT or after the last emapalumab-lzsg infusion.

In study NI-0501-04, treatment duration was up to 8 weeks after which patients could continue treatment on the extension study. All patients received an initial starting dose of 1 mg/kg every 3 days. Subsequent doses could be increased to a maximum of 10 mg/kg based on clinical and laboratory parameters. Forty-four percent of patients remained at a dose of 1 mg/kg, 30% of patients increased to 3-4 mg/kg, and 26% of patients increased to 6-10 mg/kg. The median time to dose increase was 27 days (range: 3-31 days) with 22% of patients requiring a dose increase in the first week of treatment.

In the trial, all patients received dexamethasone as background HLH treatment with doses between 5-10 mg/m² per day. Cyclosporine A was continued if administered prior to screening. Patients receiving intrathecal methotrexate and glucocorticoids at baseline could continue these therapies. In study NI-0501-04, the median patient age was 1 year (0.2 to 13). Fifty-nine percent of the patients were females, 63% were Caucasian, 11% were Asian, and 11% were Black. A genetic mutation known to cause HLH was present in 82% of patients.

The efficacy of emapalumab-lzsg was based on overall response rate (ORR) at the end of treatment, defined as achievement of either a complete response (CR), or partial response (PR), or HLH improvement. ORR was evaluated using an algorithm that included the following objective clinical and laboratory parameters: fever, splenomegaly, CNS symptoms, complete blood count, fibrinogen and/or D-dimer, ferritin, and soluble CD 25 levels. CR was defined as normalization of all HLH abnormalities (i.e., no fever, no splenomegaly, neutrophils >1x10⁹/L, platelets >100x10⁹/L, ferritin <2000 µg/L, fibrinogen >1.5 g/L, D-dimer <500 µg/L, normal CNS symptoms, no worsening of sCD25 > 2-fold baseline). PR was defined as normalization of ≥ 3 HLH abnormalities. HLH improvement was defined as ≥ 3 HLH abnormalities improved by at least 50% from baseline. The ORR at the end of treatment is shown at Table 1.

Table 1 ORR at End of Treatment^c

N=27, Overall response		ORR, N(%)
Complete response, n (%)	7 (26%)	17 (63%)
Partial response	8 (30%)	(95% confidence interval) (0.42,0.81)

^c Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

HLH improvement	2 (7.4 %)	p-value 0.013
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The median duration of response, defined as time to loss of first response is not reached (range: 4 to 56+ days for patients who lost initial response). Seventy percent (19/27) of patients proceeded to HSCT.

5 Risk Assessment & Safe-Use Conditions^d

The safety data included 34 patients with untreated primary HLH (7 patients) and previously treated patients (27 patients in Study NI-0501-04) received emapalumab-lzsg at a starting dose of 1 mg/kg every 3 days with dose increases up to 10 mg/kg. The median duration of therapy with emapalumab-lzsg was 59 days (range: 4 to 245 days) and the median cumulative dose was 25 mg/kg (range: 4 to 254 mg/kg). The median age of study population was 1 year (range: 0.1 to 13 years), 53% were female, and 65% were Caucasian.

Deaths:⁸

There were 11 deaths (29%) reported in the safety data. Eight deaths occurred pre-transplant and 3 deaths occurred post-transplant. There was one death due to histoplasmosis before transplant that was possibly related to study treatment. The causes of deaths were histoplasmosis, multi-organ failure (2 deaths), septic shock, gastrointestinal hemorrhage, respiratory failure, neurologic deterioration, cytomegavirus pneumonitis, and death during conditioning.

The serious risks reported in the safety database were discussed as below. If approved, these risks will be communicated in the warnings and precautions sections of the label, as well as in a Medication Guide.

5.1 INCREASE RISKS OF FATAL AND SERIOUS INFECTIONS

Due to its mechanism of action, neutralize IFN γ , emapalumab-lzsg may increase the risk of fatal and serious infections. This risk includes infections caused by mycobacteria, Herpes zoster virus, and *Histoplasma capsulatum*.

In the clinical trial, serious infections such as sepsis, pneumonia, bacteremia, disseminated histoplasmosis, necrotizing fasciitis, viral infections, were reported in 32% of patients. The reported infections were viral (41%), bacterial (35%), fungal (9%), and pathogen was not identified in 15% of cases.

^d Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

In the warnings and precautions section of prescribing information, if emapalumab-lzsg is approved, healthcare providers (HCPs) will be advised to administer prophylaxis for herpes zoster, *Pneumocystis jiroveci*, and fungal infections to mitigate the risk to patients while receiving emapalumab-lzsg. HCPs will also be advised to evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating emapalumab-lzsg, as well as to monitor patients for signs or symptoms of infection and treat as appropriate with antimicrobial therapy.

5.2 DO NOT ADMINISTER LIVE OR LIVE ATTENUATED VACCINES DUE TO INCREASE RISK OF INFECTION

If emapalumab-lzsg is approved, HCPs will be advised in the warnings and precautions section of the label not to administer live or live attenuated vaccines to patients while receiving emapalumab-lzsg and for at least 4 weeks after the last dose of emapalumab-lzsg.

5.3 INFUSION-RELATED REACTIONS

Twenty-seven percent of patients who received emapalumab-lzsg were reported to have infusion-related reactions, including drug eruption, pyrexia, rash, erythema, and hyperhidrosis. The proposed labeling will advise HCPs in the warnings and precautions section to monitor patients for infusion related reactions, as well as to interrupt the infusion for severe infusion reactions and institute appropriate medical management prior to continuing infusion.

6 Expected Postmarket Use

Emapalumab-lzsg, if approved, will be administered in treatment centers and hospitals and the likely prescribers will be oncologists/hematologists and pediatric oncologists/hematologists.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for emapalumab-lzsg beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of emapalumab-lzsg on the basis of the efficacy and safety information currently available.⁹

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for emapalumab-lzsg, DRISK considers patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population.

The incidence of HLH is reported to be 1.2 cases per million persons per year. However, unpublished observations estimate that the figures have slightly increased over time because of improved detection. This amounts to 1 case per every 50,000 births.

Untreated patients with HLH have a survival of months, due to progressive multi-organ failure. Those with an inherited mutation in an HLH gene have a survival of about 2 months without treatment. In a series of 162 adults with HLH, 94 (58%) patients survived. Of the patients who did not survive, about half died within one month of diagnosis, especially those with hematologic malignancies. Even with treatment survival is poor, only 21-26% are expected to survive 5 years.

The most concerning adverse reaction associated with emapalumab-lzsg is the risk of serious and fatal infections due to pathogens favored by IFN γ neutralization. These pathogens include mycobacteria, herpes zoster, *hispoplasma capsulatum*, *Pneumocystis jirovecii*, and fungi. This risk will be communicated in the prescribing information in the warnings and precautions section. In addition, the prescribing information will contain instructions to prescribers regarding the need for prophylaxis against herpes zoster, *Pneumocystis jirovecii*, fungal infection, and tuberculosis (if the patient is at risk for tuberculosis), as well as close monitoring for signs and symptoms of infection and initiation of appropriate antimicrobial therapy in the event of an infection. Other adverse events, such as an increased risk of infection with the use of live virus vaccines and infusion-related reactions will be described in the warnings and precautions section of the label. Additionally, labeling will include a Medication Guide.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable, therefore, a REMS is not necessary for emapalumab-lzsg to ensure its benefits outweigh its risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

¹ McClain KL & Eckstein O, Clinical features and diagnosis of hemophagocytic lymphohistiocytosis, www.uptodate.com, accessed 3/29/2018

² Hemophagocytic lymphohistiocytosis, <https://rarediseases.info.nih.gov/diseases/6589/hemophagocytic-lymphohistiocytosis>, accessed 6/20/2018

³ McClain KL, Treatment and prognosis of hemophagocytic lymphohistiocytosis, www.uptodate.com, accessed 3/29/2018

⁴ Schwartz RA, Hemophagocytic lymphohistiocytosis, <https://emedicine.medscape.Com/article/986458-overview>, accessed 3/29/2018

⁵ Schwartz RA, Hemophagocytic lymphohistiocytosis, <https://emedicine.medscape.Com/article/986458-overview>, accessed 3/29/2018

⁶ McClain KL, Treatment and prognosis of hemophagocytic lymphohistiocytosis, www.uptodate.com, accessed 3/29/2018

⁷ Proposed labeling of emapalumab, October 18, 2018

⁸ Dr. Merion, M. emapalumab-lzsg clinical mid-cycle presentation, June 25, 2018

⁹ Dr. Merion, M. emapalumab-lzsg clinical mid-cycle presentation, June 25, 2018

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