Keystone First VIP Choice

Medical Policy Bulletin
Title:
Emapalumab-lzsg (Gamifant®)
Policy #:
MA08.104b

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

MEDICALLY NECESSARY

Emapalumab-lzsg (Gamifant®) is considered medically necessary and, therefore, covered for the treatment of pediatric (newborn and above) and adult individuals with the diagnosis of primary hemophagocytic lymphohistiocytosis (HLH) when all of the following criteria are met, including dosing and frequency:

- Diagnosis of primary HLH confirmed by criteria described below*
- Individual has refractory, recurrent, or progressive disease
- Individual has a documented failure, contraindication, or intolerance to conventional HLH therapy (i.e., dexamethasone and etoposide (VP-16). Intrathecal methotrexate and hydrocortisone for those with central nervous system disease)
- Individual has body weight of 3 kilograms or more
- Emapalumab-lzsg (Gamifant®) is not administered concurrently with any biologic
- Dosing and frequency:
    - Initial dosing: 1 mg/kg IV infusion twice per week (every 3 to 4 days); titration, may increase to 3 mg/kg on Day 3 or to 6 mg/kg on Day 6 onwards for unsatisfactory improvement in clinical condition and at least one of the following:
        - Fever persistence/recurrence, splenomegaly worsening, coagulopathy (D-dimer abnormal at baseline and not improved plus fibrinogen at less than 100 mg/dL); ferritin less than 20 percent decrease from baseline of 3000 ng/mL or greater or any increase above 3000 ng/mL from baseline below 3000 ng/mL; neutrophil count not improved to above 500/mm from baseline of less than 500/$mm^{(3)}$ or decreased to less than 500 $mm^{(3)}$ from baseline of 500 to 1000/$mm^{(3)}$ or decreased to less than 1000/$mm^{(3)}$ from baseline of 1000 to 1500/$mm^{(3)}$; platelet count not improved to more than 50,000/$mm^{(3)}$ from baseline of less

than 50,000/mm$^{(3)}$ or less than 30 percent improvement from baseline of greater than 50,000/mm$^{(3)}$ or any decrease to under 100,000/mm$^{(3)}$ from baseline greater than 100,000/mm$^{(3)}$
- From Day 9 onwards, may increase to 10 mg/kg dose if clinically indicated; decrease dose to previous level once stabilized
- Continuation: administer until hematopoietic stem cell transplantation is performed or until unacceptable toxicity; discontinue when individual no longer requires therapy for treatment of the condition
- Emapalumab-lzsg (Gamifant®) must be administered with dexamethasone

*The diagnosis of FHL is made based on the presence of clinical criteria and is confirmed by molecular genetic testing for this autosomal recessive disease. Five disease subtypes (FHL1, FHL2, FHL3, FHL4, and FHL5) are described in the literature and can be inherited in a homozygous or compound heterozygous pattern. Four genes in which pathogenic variants are causative have been identified: PRF1 (FHL2), UNC13D (FHL3), STX11 (FHL4), and STXBP2 (FHL5).

Examples of pathogenic variants for PRF1 include but not limited to: p.54R > C/91A > V and p.47G > V

Examples of pathogenic variants for UNC13D include but not limited to : c.118-308C>T and (253-kb inversion)

Examples of pathogenic variants for STX 11 include but not limited to : 73 G > T (E25X) and 106G > C (E36Q)

Examples of pathogenic variants for STXBP2 include but not limited to : c.1430C>T, and c.1214G>A

In adults, diagnosis confirmed by heterozygosity of one of the above genes together with clinical findings associated with HLH OR five of the following eight findings:
- Prolonged fever (more then seven days) ≥101.3°F
- Splenomegaly
- Peripheral blood cytopenia, with at least two of the following: hemoglobin <9 g/dL (for infants <4 weeks, hemoglobin <10 g/dL); platelets <100,000/microL; absolute neutrophil count <1000/microL
- Hypertriglyceridemia (fasting triglycerides >265 mg/dL) and/or hypofibrinogenemia (fibrinogen <150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent NK cell activity
- Ferritin >500 ng/mL (the author prefers to consider a ferritin >3000 ng/mL as more indicative of HLH [81])
- Elevated soluble CD25 (soluble IL-2 receptor alpha [sIL-2R]) two standard deviations above age-adjusted laboratory-specific norms

EXPERIMENTAL/INVESTIGATIONAL

All other uses for emapalumab-lzsg (Gamifant®) are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

DOSING AND FREQUENCY REQUIREMENTS

The Company reserves the right to modify the Dosing and Frequency Requirements listed in this policy to ensure consistency with the most recently published recommendations for the use of emapalumab-lzsg (Gamifant®). Changes to these guidelines are based on a consensus of information obtained from resources such as, but not limited to: the US Food and Drug Administration (FDA); Company-recognized authoritative pharmacology compendia; or published peer-reviewed clinical research. The professional provider must supply supporting documentation (i.e., published peer-reviewed literature) in order to request coverage for an amount of emapalumab-lzsg (Gamifant®) outside of the Dosing and Frequency Requirements listed in this policy. For a list of Company-recognized pharmacology compendia, view our policy on off-label coverage for prescription drugs and biologics.

Accurate member information is necessary for the Company to approve the requested dose and frequency of emapalumab-lzsg (Gamifant®). If the member's dose, frequency, or regimen changes (based on factors such as changes in member weight or incomplete therapeutic response), the provider must submit those changes to the Company for a new approval based on those changes as part of the utilization management activities. The Company reserves the right to conduct post-payment review and audit procedures for any claims submitted for emapalumab-lzsg (Gamifant®).

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

When coverage of emapalumab-lzsg (Gamifant®) is requested outside of the Dosing and Frequency Requirements listed in this policy, the prescribing professional provider must supply documentation (i.e., published peer-reviewed literature) to the Company that supports this request.

Guidelines

DRUG INFORMATION

In accordance with US Food and Drug Administration (FDA) prescribing information, emapalumab-lzsg (Gamifant®) is administered as an intravenous infusion over 1 hour twice per week (every three to four days) 1 mg/kg. Doses subsequent to the initial dose may be increased based on clinical and laboratory criteria. Administer until hematopoietic stem cell transplantation (HSCT) is performed or individual experiences unacceptable toxicity.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable Evidence of Coverage, emapalumab-lzsg (Gamifant®) is covered under the medical benefits of the Company’s Medicare Advantage products when the medical necessity criteria and dosing and frequency requirements listed in this medical policy are met.

CONVENTIONAL THERAPY FOR HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

Induction therapy based on the HLH-94 protocol consists of a series of weekly treatments with dexamethasone and etoposide (VP-16). Intrathecal methotrexate and hydrocortisone are given to those with central nervous system disease. After induction, individuals 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, central nervous system disease, or disease relapse.

US FOOD AND DRUG ADMINISTRATION (FDA) STATUS

Emapalumab-lzsg (Gamifant®) was approved by the FDA on November 20, 2018 for treatment of pediatric (newborn and above) and adult individuals with primary hemophagocytic lymphohistiocytosis (HLH) who have refractory, recurrent or progressive disease, or intolerance with conventional HLH therapy.

Description

Primary hemophagocytic lymphohistiocytosis (HLH) is an inherited condition in which the body's immune system attacks its own organs, including the liver, brain, and bone marrow. Untreated, the majority of children will die of the disease. Even with currently recommended therapy, HLH is a frequently fatal condition. The early institution of therapy is critical to control the hypercytokinemia that otherwise will lead to end-organ failure and death.

The disease is classified into six different types based on genetic linkage analysis and chromosomal localization; five specific genetic defects have been identified, which account for approximately 90% of all patients. Type 1 is due to an as yet unidentified gene mutation located on chromosome nine; Type 2 is caused by mutations in the perforin (PRF1) gene; Type 3 by mutations in the Munc-13–4 (UNC13D) gene; Type 4 by mutations in the syntaxin 11 (STX11) gene; and Type 5 due to mutations in the gene encoding syntaxin binding protein 2 (STXBP-2).

Absent or decreased lymphocyte cytotoxicity is the cellular hallmark of FHL. Biochemical features such as hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia are usually present, along with high levels of soluble interleukin 2 receptor in the blood and cerebrospinal fluid. The disease is fatal unless a hematopoietic stem cell transplant (HSCT) is performed. Emapalumab-lzsg is the first and only treatment for primary hemophagocytic lymphohistiocytosis (HLH) and was FDA approved based on data from the pivotal phase 2/3 study in patients with primary HLH. The study's primary endpoint in patients with refractory, recurrent, or progressive disease during conventional HLH therapy or who were intolerant of conventional HLH therapy was achieved, with a clinically meaningful and statistically significant proportion of patients demonstrating an overall response at the end of treatment. In addition, 70 per cent of patients proceeded to hematopoietic stem-cell transplantation (HSCT).

Emapalumab-lzsg is an interferon gamma (IFNã) blocking antibody. Emapalumab-lzsg is produced in Chinese Hamster Ovary cells by recombinant DNA technology. Emapalumab-lzsg (Gamifant®) is indicated for the treatment of adult and pediatric (newborn and older) individuals with primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent, or progressive disease or intolerance with conventional HLH therapy.

PEER-REVIEWED LITERATURE

SUMMARY
The efficacy of emapalumab-lzsg (Gamifant®) was evaluated in a multicenter, open-label, single-arm trial NI0501-04 (NCT01818492) in 27 pediatric individuals with suspected or confirmed primary HLH with refractory, recurrent, or progressive disease during conventional HLH therapy or who were intolerant of conventional HLH therapy.

Twenty-seven individuals enrolled and received treatment in the study, and 20 individuals (74%) completed the study. Seven individuals (26%) were prematurely withdrawn. Twenty-two individuals (81%) enrolled in the open-label extension study, which monitored individuals for up to one year after HSCT or after the last GAMIFANT infusion (NI-0501-05; NCT02069899).

The study treatment duration was up to eight weeks, after which individuals could continue treatment on the extension study. All individuals received an initial starting dose of emapalumab-lzsg (Gamifant®) of 1 mg/kg every three days. Subsequent doses could be increased to a maximum of 10 mg/kg based on clinical and laboratory parameters interpreted as unsatisfactory response.

The efficacy of GAMIFANT was based upon overall response rate (ORR) at the end of treatment, defined as achievement of either a complete or partial response or HLH improvement. HLH improvement was defined as ≥ 3 HLH abnormalities improved by at least 50 percent from baseline. ORR was evaluated using an algorithm that included the following objective clinical and laboratory parameters: fever, splenomegaly, central nervous system symptoms, complete blood count, fibrinogen and/or D-dimer, ferritin, and soluble CD25 (also referred to as soluble interleukin-2 receptor) levels. Complete response was defined as normalization of all HLH abnormalities (i.e., no fever, no splenomegaly, neutrophils > $1x10^9$/L, platelets > $100x10^9$/L, ferritin < 2,000 g/L, fibrinogen > 1.50 g/L, D-dimer < 500 ug/L, normal CNS symptoms, no worsening of sCD25 > 2-fold baseline). Partial response was defined as normalization of ≥ 3 HLH abnormalities. HLH improvement was defined as ≥ 3 HLH abnormalities improved by at least 50% from baseline. CR was achieved by 26 percent, PR by 30 percent, and HLH improvement by 7.4 percent.

OFF-LABEL INDICATION

There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company's off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

References

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)
N/A

ICD - 10 Procedure Code Number(s)
N/A

ICD - 10 Diagnosis Code Number(s)
D76.1 Hemophagocytic lymphohistiocytosis

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HCPCS Level II Code Number(s)
J9210 Injection, emapalumab-lzsg, 1 mg

Revenue Code Number(s)
N/A

Policy History

Revisions From MA08.104b:

05/07/2024	This policy has been reissued in accordance with the Company's annual review process.
09/05/2023	This policy has been reissued in accordance with the Company's annual review process.
06/29/2022	This policy has been reissued in accordance with the Company's annual review process.
05/05/2021	This policy has been reissued in accordance with the Company's annual review process.
04/08/2020	This policy has been reissued in accordance with the Company's annual review process.
10/01/2019	This policy has been identified for the HCPCS code update, effective 10/01/2019. The following HCPCS codes have been **termed** from this policy: C9050 Injection, emapalumab-lzsg, 1 mg J3590 Unclassified biologic The following HCPCS code has been **added** to this policy: J9210 Injection, emapalumab-lzsg, 1 mg

Revisions From MA08.104a:

07/01/2019	This policy has been identified for the HCPCS code update, effective 07/01/2019. The following HCPCS code has been **added** to this policy: C9050 Injection, emapalumab-lzsg, 1 mg The following HCPCS code has been **removed** from this policy: C9399 Unclassified drugs or biologicals

Revisions From MA08.104:

02/25/2019	This new policy has been developed to communicate the Company’s coverage criteria for Emapalumab-lzsg (Gamifant®), including dosing and frequency.

Version Effective Date:
10/01/2019
Version Issued Date:
10/02/2019
Version Reissued Date:
05/07/2024