Drug Coverage Policy

Effective Date.....5/1/2025
Coverage Policy Number.....IP0405
Policy Title.....Enjaymo

Hematology – Enjaymo

- Enjaymo® (sutimlimab-jome intravenous infusion – Bioverativ/Sanofi)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Medical Necessity Criteria

Documentation: Documentation is required where noted in the criteria. Documentation may include, but not limited to, chart notes, laboratory tests, medical test results, claims records, prescription receipts, and/or other information.

Enjaymo is considered medically necessary when the following criteria are met:

1. **Cold Agglutinin Disease.** Individual meets **ALL** of the following criteria:
   A. Age 18 years or older
   B. Weighs 39 kg or more
   C. History of at least **ONE** symptom associated with cold agglutinin disease
   D. Documentation provided evidence of chronic hemolysis
   E. Patient meets **BOTH** of the following diagnostic criteria:

i. Documentation provided that patient has direct antibody test strongly positive for C3d and negative or only weakly positive for immunoglobulin G
ii. Documentation provided that patient has cold agglutinin antibody titer is greater than 64 at 4°C (approximately 40°F)

F. Patient meets **BOTH** of the following (at baseline prior to treatment):
i. Documentation provided that patient has hemoglobin less than or equal to 10 g/dL
ii. Documentation provided that patient has total bilirubin above the upper limit of normal based on the reference range for the reporting laboratory

G. Secondary causes of cold agglutinin syndrome have been excluded
H. Medication is prescribed by, or in consultation with, a hematologist

Dosing. ONE of the following dosing regimens:
1. Weight of 75 kg or more: The dose is 7,500 mg intravenously not more frequently than once weekly
2. Weight of 39 kg to less than 75 kg: The dose is 6,500 mg intravenously not more frequently than once weekly

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Reauthorization Criteria

Continuation of sutimlimab-jome (Enjaymo) is considered medically necessary for cold agglutinin disease when the above medical necessity criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial approval duration: up to 12 months
Reauthorization approval duration: up to 12 months

Conditions Not Covered

Any other use is considered not medically necessary, including the following (this list may not be all inclusive):

1. **Paroxysmal Cold Hemoglobinuria:** Insufficient information exists from controlled trials and evidence based professional organizations on sutimlimab-jome (Enjaymo) for paroxysmal cold hemoglobinuria.

Coding Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J1302	Injection, sutimlimab-jome, 10 mg

Background

OVERVIEW
Enjaymo, a classical complement inhibitor, is indicated for the treatment of hemolysis in cold agglutinin disease in adults.[1]

Disease Overview
Cold agglutinin disease is a rare form of autoimmune hemolytic anemia with a prevalence of about 16 per million and an incidence of 1 per million year.[2-4,10] Primary cold agglutinin disease is a B-cell lymphoproliferative disorder in which autoantibodies are produced against erythrocyte surface antigens. Primary cold agglutinin disease is distinct from secondary disease, termed cold agglutinin syndrome, which can occur with underlying conditions such as malignancy, infection, and autoimmune diseases.[2,3] Diagnosis of cold agglutinin disease is defined by chronic hemolysis, a cold agglutinin titer ≥ 64 at 4°C, and typical findings on direct antibody test (DAT), which include strong positivity for complement protein C3d and negativity (or only weak positivity) for immunoglobulin G.[2-4] Secondary causes of cold agglutinin syndrome should be excluded. Importantly, patients without chronic hemolysis or circulatory symptoms do not have cold agglutinin disease, even in the presence of positive DAT.[2] Symptoms include cold-induced circulatory symptoms, which can range from slight acrocyanosis to severe Raynaud phenomena. Anemia is generally considered mild to moderate with a median hemoglobin (Hb) of 8.9 g/dL; however, the lower tertile Hb was 8.0 g/dL and ranged to as low as 4.5 g/dL.[2,4]

Clinical Efficacy
In the CARDINAL trial, patients (n = 24) were required to have a confirmed diagnosis of cold agglutinin disease based on chronic hemolysis, typical DAT findings, and a recent blood transfusion within the prior 6 months.[1,5-7] Patients were also required to have a baseline hemoglobin level < 10 g/dL and total bilirubin above normal. Approximately two-thirds of patients had failed other therapies (e.g., rituximab). The Phase III CADENZA trial (n = 42) also required chronic hemolysis, as well as the DAT and cold agglutinin titer findings described above; however, recent history of blood transfusion was not required.[1,8]

Dosing Information
Dosing is weight-based and is provided for patients weighing ≥ 39 kg.[1] For a patient weighing 39 to < 75 kg, the recommended dose is 6,500 mg. For a patient weighing ≥ 75 kg, the dose is 7,500 mg. For all patients, the initial dosing frequency is once weekly for 2 weeks, with administration once every 2 weeks (Q2W) thereafter. However, if the interval between doses exceeds 17 days, Enjaymo should be administered once weekly for 2 weeks, returning to Q2W administration thereafter.

Guidelines
An international consensus guideline for autoimmune hemolytic anemias was published in 2020.[9] The guideline was published prior to the approval of Enjaymo, and no formal recommendation is made regarding its place in therapy, although positive Phase I data are acknowledged. It is noted that clinical and histological assessment, as well as radiologic examinations as needed, are necessary to rule out cold agglutinin syndrome secondary to malignant disease. Treatment of cold

agglutinin syndrome involves supportive care and management of the underlying disease. For treatment of cold agglutinin disease, asymptomatic patients should be managed with watchful waiting. For symptomatic patients (i.e., those with anemia, transfusion, or circulatory symptoms), rituximab is the best-documented first-line treatment and may be given alone or in combination with bendamustine. For second-line treatment, the combination of rituximab plus bendamustine is recommended (if not given in the first-line setting). Alternatively, rituximab monotherapy may be repeated for patients who previously responded for at least 1 year. Rituximab plus fludarabine is an option for fit, elderly patients. There are no evidence-based therapies for the third-line setting.

References

1. Enjaymo® intravenous infusion [prescribing information]. Waltham, MA: Bioverativ/Sanofi; March 2023.
2. Berentsen S, Röth A, Randen U, et al. Cold agglutinin disease: current challenges and future prospects. *J Blood Med*. 2019; 10:93-103.
3. Berentsen S. How I treat cold agglutinin disease. *Blood.* 2021;137(10):1295-1303.
4. Swiecicki PL, Hegerova LT, Gertz MA. Cold agglutinin disease. *Blood*. 2013;122(7):1114-1121.
5. Röth A, Barcellini W, D'Sa S, et al. Sutimlimab in cold agglutinin disease. *N Engl J Med*. 2021;384(14):1323-1334.
6. Röth A, Broome CM, Barcellini W, et al. Long-term sutimlimab improves quality of life for patients with cold agglutinin disease: CARDINAL 2-year follow-up. *Blood Adv*. 2023;7(19):5890-5897.
7. Röth A, Barcellini W, D'Sa S, et al. Sustained inhibition of complement C1s with sutimlimab over 2 years in patients with cold agglutinin disease. *Am J Hematol*. 2023;98(8):1246-1253.
8. Röth A, Berentsen S, Barcellini W, D'Sa S, et al. Sutimlimab in patients with cold agglutinin disease: results of the randomized placebo-controlled phase 3 CADENZA trial. *Blood*. 2022;140(9):980-991.
9. Jäger U, Barcellini W, Broome CM, et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: recommendations from the First International Consensus Meeting. *Blood Rev*. 2020 May; 41:100648.
10. Barcellini W, Fattizzo B. The evolving management algorithm for a patient with newly diagnosed cold agglutinin disease. *Expert Rev Hematol*. 2024;17(7):287-294.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	No criteria changes.	5/1/2024
Annual Revision	Added definition of "documentation". Updated "documentation" phrasing throughout coverage policy.	5/1/2025

The policy effective date is in force until updated or retired.