PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Enjaymo Prior Authorization Policy
- Enjaymo® (sutimlimab-jome intravenous infusion – Bioverativ/Sanofi)

REVIEW DATE: 01/03/2024

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 autoimmune hemolytic anemia.[2-4] 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 pivotal CARDINAL trial (published) [n = 24], patients 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 (published) [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]

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.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Enjaymo. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Enjaymo as well as the monitoring required for adverse events and long-term efficacy, approval requires Enjaymo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Enjaymo is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Cold Agglutinin Disease.** Approve for 1 year if the patient meets the following (A, B, C, D, E, F, G, and H):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient weighs ≥ 39 kg; AND
   - **C)** Patient has a of at least one sign or symptom associated with cold agglutinin disease; AND
     Note: Examples include symptomatic anemia (e.g., anemia associated with fatigue, weakness, shortness of breath, heart palpitations, lightheadedness, chest pain), acrocyanosis, Raynaud's syndrome, hemoglobinuria, disabling circulatory symptoms, or a major adverse vascular event (e.g., thrombosis).
   - **D)** According to the prescriber, the patient has evidence of chronic hemolysis; AND
   - **E)** Patient meets the following diagnostic criteria (i and ii):
     - **i.** Direct antibody test strongly positive for C3d and negative or only weakly positive for immunoglobulin G; AND
     - **ii.** Cold agglutinin antibody titer ≥ 64 at 4°C (approximately 40°F); AND
   - **F)** At baseline (prior to the initiation of Enjaymo), patient meets both of the following (i and ii):
     - **i.** Hemoglobin ≤ 10 g/dL; AND
     - **ii.** Total bilirubin above the upper limit of normal, based on the reference range for the reporting laboratory; AND
   - **G)** According to the prescriber, secondary causes of cold agglutinin syndrome have been excluded; AND
     Note: Examples of secondary causes of cold agglutinin syndrome include infection, rheumatologic diseases, and active hematologic malignancies.
   - **H)** Enjaymo is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Enjaymo is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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.
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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.
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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.