Policy Number	**RX501.180**
Policy Effective Date	**5/7/2026**

Sutimlimab-jome

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of care developed by: nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Sutimlimab-jome (Enjaymo®) **may be considered medically necessary** for the treatment of hemolysis when the individual meets the below criteria:

1. Adults with a diagnosis of cold agglutinin disease confirmed by the following:
    a. Chronic hemolysis; AND
    b. Positive polyspecific direct antiglobulin test (DAT); AND
    c. Monospecific direct antiglobulin test (DAT) specific for C3d; AND
    d. Cold agglutinin titer ≥64 at 4°C; AND
2. Cold agglutinin syndrome is not secondary to infection, rheumatologic disease, systemic lupus erythematosus (SLE), other autoimmune disorders with anti-nuclear antibodies, or overt hematologic malignancy.

Sutimlimab-jome (Enjaymo) **is considered experimental, investigational and/or unproven** for all other non-approved U.S. Food and Drug Administration indications.

Policy Guidelines

Individuals should be vaccinated against encapsulated bacteria, including *Streptococcus pneumoniae* and *Neisseria meningitidis* (serogroups A, C, W, Y and B), according to current Advisory Committee on Immunization Practices (ACIP) recommendations at least 2 weeks prior to initiation of Enjaymo. (1)

If urgent Enjaymo therapy is indicated in a patient who is not up to date with vaccines for *Streptococcus pneumoniae* and *Neisseria meningitidis,* administer these vaccines as soon as possible. (1)

Description

Cold agglutinin disease is a rare autoimmune disorder characterized by the premature destruction of red blood cells (hemolysis). More specifically, CAD is a subtype of autoimmune hemolytic anemia. In this type of disorder, red blood cells are "tagged" by antibodies and are then destroyed by other types of immune cells. The disease is termed "cold" because the antibodies are active and cause hemolysis at cold temperatures, usually 3° to 4°C (37° to 39°F), which is not necessarily the case in other types of autoimmune hemolytic anemia. (2, 3)

CAD affects about one person per million every year and mostly develops between the ages of 40 and 80 years. The disease is present in about 16 people per million (prevalence) and develops in one person per million every year (incidence). The disease is almost twice as common in women compared to men. Those living with conditions associated with CAD are more likely to develop the disease. CAD is also potentially more common, or at least more recognized, in colder climates. (2, 3)

CAD occurs when antibodies produced by the immune system bind to red blood cells and identify them as targets. Antibodies are specialized proteins that bind to invading organisms and contribute to their destruction. There are five main classes of antibodies: IgA, IgD, IgE, IgG, and IgM. Most cases of CAD are due to IgM antibodies. When antibodies attack healthy tissue, they may be referred to as autoantibodies. In the case of CAD, these autoantibodies are active and can trigger hemolysis when they are exposed to cold temperatures. Once red blood cells are "tagged" by a cold-induced antibody, they can clump (agglutinate) and are then bound by another component of the immune system known as complements. Once red blood cells are bound to complements, they are attacked and destroyed by different types of immune cells, such as macrophages. (2, 3)

CAD may also occur as a secondary disorder in association with several different underlying disorders such as certain infectious diseases (e.g., mycoplasma infection, mumps, cytomegalovirus, infectious mononucleosis), immunoproliferative diseases (e.g., non-Hodgkin's lymphoma, chronic lymphocytic leukemia, monoclonal gammopathy of unknown significance), or connective tissue disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus). A secondary cause of CAD might be present in up to 70% of affected individuals. (2, 3)

The symptoms associated with the disease are mostly the result of either hemolysis or circulatory symptoms, both of which are triggered by exposure to cold temperatures. Some individuals, especially those with mild hemolysis and a gradual onset of anemia, may not have any obvious symptoms (asymptomatic). Symptoms of anemia include paleness of the skin (pallor), fatigue, shortness of breath (dyspnea), dizziness and palpitations. In cases of brisk and severe hemolysis, chest pain, decreased alertness (lethargy), confusion, transient loss of consciousness (syncope), and deregulation of heart rate and blood pressure (hemodynamic instability) might occur. Hemolysis also leads to increased release of hemoglobin (an oxygen-carrying protein) in the blood and urine, which can result in darkly pigmented urine. (2, 3)

Hemoglobin is degraded into a yellow compound called bilirubin, which can accumulate and lead to yellowing of the skin and whites of the eyes (jaundice). Circulatory symptoms seen in CAD include coldness of the fingers and/or toes (digits) and painful bluish or reddish discoloration of the skin of the digits, ankles, and wrists (acrocyanosis or Raynaud phenomenon). In severe cases, ulcers may develop on the extremities of digits. There is a possibility that people living with CAD are at a higher risk of developing blood clots, although more studies are needed to clarify this potential association. CAD can be a long-standing (chronic) disease, but can be self-limited and clinically silent, especially when associated with infectious diseases; although it can be caused by severe diseases, CAD itself does not seem to be associated with a significantly decreased life expectancy. (2, 3)

Sutimlimab-jome (Enjaymo) is an immunoglobulin G (IgG), subclass 4 (IgG4) monoclonal antibody (mAb) that inhibits the classical complement pathway and specifically binds to complement protein component 1, s subcomponent (C1s), a serine protease which cleaves C4. (1)

Regulatory Status
In 2022, the U.S. Food and Drug Administration approved sutimlimab-jome (Enjaymo®) to decrease the need for red blood cell transfusion due to hemolysis (red blood cell destruction) in adults with cold agglutinin disease. (1)

Rationale

This policy is based on the U.S. Food and Drug Administration prescribing information for sutimlimab-jome (Enjaymo). (1)

Sutimlimab-jome (Enjaymo)
CADENZA Trial
The efficacy of Enjaymo was assessed in a placebo-controlled 6-month trial in 42 patients (CADENZA, NCT 03275454). Following the completion of the 6-month treatment period (Part A) in which 22 patients received Enjaymo, and 20 patients received placebo, 39

patients (19 patients on Enjaymo and 20 patients on placebo) continued to receive Enjaymo in a long-term safety and durability of response extension phase (Part B) for an additional 12 months following last patient out from Part A. The trial included a 9-week safety follow-up after the last dose of Enjaymo. Patients with a confirmed diagnosis of cold agglutinin disease (CAD) based on chronic hemolysis, poly-specific direct antiglobulin test (DAT), monospecific DAT specific for C3d, cold agglutinin titer ≥64 at 4°C, an IgG DAT ≤1+ and no history of transfusion within 6 months, or more than one blood transfusion in the 12 months prior to enrollment in the trial were administered 6.5 g or 7.5 g Enjaymo (based on body weight) intravenously over approximately 60 minutes on Day 0, Day 7, and every 14 days thereafter; or placebo. Patients with cold agglutinin disease secondary to infection, rheumatologic disease, systemic lupus erythematosus, or overt hematologic malignancy were excluded, whereas patients with a history of or concomitant low-grade lymphoproliferative disease were not excluded.

Major baseline characteristics of the study population are summarized in Table 1.

Table 1. Baseline Characteristics of Patients Included in CADENZA

Parameter	**Statistic**	**CADENZA**	
		Placebo N=20	**Enjaymo N=22**
Age	Mean Min, Max	68.2 51, 83	65.3 46, 88
Sex Male Female	 n (%)	 4 (20.0) 16 (80.0)	 5 (22.7) 17 (77.3)
Body Weight	Mean, Kg Min, Max	64.9 48, 95	66.8 39, 100
Hemoglobin	Mean, g/dL	9.33	9.15
Bilirubin (total)[a]	µmol/L	35.77 (1.75 x ULN)	41.17 (2 X ULN)
LDH	U/L	380.8	421.5
History of transfusion Within last 6 months Within last 12 months	Mean number of transfusions (range)	0 0	0 0.14 (0, 1)
FACIT[b]-Fatigue scale	Mean	32.99	31.67

[a] Placebo N=18 and Enjaymo N=20 in CADENZA, for bilirubin data excluding patients with either a positive or no available test result for Gilbert's syndrome.

[b] Functional Assessment of Chronic Illness Therapy (FACIT-Fatigue is measured on a scale of 0 (worst fatigue) to 52 (no fatigue).

FACIT-Fatique: Functional Assessment of Chronic Illness Therapy; g/dL: grams per deciliter; kg: kilogram; LDH: lactate dehydrogenase; µmol/L: micromoles per liter; U/L: microliter; Min: minimum; Max: maximum; ULN: upper limit of normal.

Efficacy was based on the proportion of patients who met the following criteria: an increase from baseline in hemoglobin (Hgb) level ≥1.5 g/dL at the treatment assessment time point (mean value from Weeks 23, 25, and 26), no blood transfusion from Week 5 through Week 26, and no treatment for CAD beyond what was permitted per protocol from Week 5 through Week 26. Efficacy was further assessed based on the effect of Enjaymo on Hgb, laboratory measures of hemolysis including mean change from baseline in total bilirubin and lactate dehydrogenase (LDH). Supportive efficacy data collected included transfusion usage after five weeks of treatment. In addition, mean change from baseline in symptoms and impacts of fatigue were assessed using a patient-reported outcome instrument, the Functional Assessment of Chronic Illness Therapy (FACIT-Fatigue) (score range from 0 to 52 with higher scores indicating less fatigue).

The data from this study demonstrated a statistically significant treatment effect of Enjaymo over placebo in terms of the rate of patients who met the efficacy criteria (responder) as well as improving symptoms and impacts of fatigue (FACIT-Fatigue). The responder rate difference between Enjaymo and placebo was 58.78% (95% confidence interval [CI]: 34.6% to 82.96%) with a p-value of 0.0004. At the treatment assessment timepoint (TAT), 16 of 22 patients on Enjaymo (72.7%; 95% CI: 49.8% to 89.3%) and 3 of 20 patients on placebo (15.0%; 95% CI: 3.2% to 37.9%) met primary criteria. Efficacy of Enjaymo in the inhibition of hemolysis in patients with CAD was demonstrated across multiple end points as described in the table below (see Table 2).

Table 2. Efficacy Results in Patients with CAD in the CADENZA Part A Study

Parameter	**Statistic**	**Placebo N=20**	**Enjaymo N=22**	**Treatment Effect**
Responder[a]	n (%)	3 (15)	16 (72.7)	58.378 (34.6, 82.96)[b]
	p-value			<0.001
Hemoglobin	Mean change from baseline (LS Mean), g/dL	0.09	2.66	2.56
	95% CI of LS Mean			(1.75, 3.38)
	p-value			<0.001
Patients with mean change from baseline of greater than	n (%)	3 (15)	16 (72.7)	NC

or equal to 1.5 g/dL				
Patients not receiving blood transfusion from Week 5 through Week 26 (transfusion avoidance)	n (%	16 (80)	18 (81.8)	NC
Patients not receiving protocol-prohibited CAD medications from Week 5 through Week 26[c]	n (%)	20 (100)	19 (86.4)	NC
FACIT - Fatigue	Mean change from baseline (LS Mean)	1.91	10.83	8.93
	95% CI of LS Mean			(4, 13.85)
	p-value			<0.001

[a] A responder was defined as a patient with an increase from baseline in Hgb level ≥ 1.5 g/dL at the treatment assessment time point (mean value from Weeks 23, 25, and 26), no blood transfusion from Week 5 through Week 26, and no treatment for CAD beyond what was permitted per protocol from Week 5 through Week 26.
[b] The Mantel-Haenszel stratum-weighted estimator of the rate difference with 95% CI was calculated using the Sato variance estimator. The stratification factors are baseline hemoglobin (< median vs ≥ median) and geographic region (Asia/Other, North America, and Europe)
[c] Prohibited therapies included rituximab alone or in combination with cytotoxic agents.
CAD: cold agglutinin disease; CI: confidence interval; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue Scale; g/dL: grams per deciliter; LS: least square; NC: not calculated.

During Part A, an increase in mean hemoglobin level of 2.02 g/dL was observed in patients on Enjaymo at Week 3; in the placebo group the mean hemoglobin level decreased by 0.31 g/dL. At treatment assessment timepoint, a mean decrease in bilirubin of 1.29 mg/dL compared to baseline was reported in patients on Enjaymo (n=17) versus 0.11 mg/dL on placebo (n=18). In the Enjaymo group, bilirubin levels normalized in 88.2% (n=15) of patients compared to 22.2% (n=4) of patients in the placebo arm. At treatment assessment timepoint, a mean decrease in LDH of 150.83 U/L compared to baseline was reported in

patients on Enjaymo (n=19) versus an increase of 7.6 U/L on placebo (n=20). In the Enjaymo group, LDH levels were <1.5 x ULN in 94.7% (n=18) of patients compared to 70% (n=14) in the placebo arm.

In Part B, mean hemoglobin levels were maintained at >10.5 g/dL. Sustained normalization of mean bilirubin levels was also observed indicating a sustained decrease in hemolysis. Mean hemoglobin level of 11.58 g/dL (range: 6.90-15.30) and 1.01 mg/dL (range: 0.29–5.54) for bilirubin was observed at the last on-treatment visit.

After the last dose of Enjaymo in the study, signs and symptoms of recurrent hemolysis were observed, nine weeks after the last dose in Part B; mean hemoglobin decreased by 2.41 g/dL (standard error [SE]: 0.373) and mean bilirubin increased by 1.27 mg/dL (SE: 0.182) from the last available values during treatment.

CARDINAL Trial

The efficacy of Enjaymo was assessed in an open-label, single-arm, 6-month trial in 24 patients (CARDINAL, NCT03347396). Following the completion of the 6-month treatment period (Part A), patients continued to receive Enjaymo in a long-term safety and durability of response extension phase (Part B) for an additional 24 months following last patient out from Part A. The trial included a 9-week safety follow-up after the last dose of Enjaymo.

Patients with a confirmed diagnosis of CAD based on chronic hemolysis, poly-specific direct antiglobulin test (DAT), monospecific DAT specific for C3d, cold agglutinin titer ≥64 at 4°C, and IgG DAT ≤1+ and a recent blood transfusion in the 6 months prior to enrollment were administered 6.5 g or 7.5 g Enjaymo (based on body weight) intravenously over approximately 60 minutes on Day 0, Day 7, and every 14 days thereafter. Patients with cold agglutinin syndrome secondary to infection, rheumatologic disease, systemic lupus erythematosus, or overt hematologic malignancy were excluded, whereas patients with a history of or concomitant low-grade lymphoproliferative disease were not excluded. Major baseline characteristics of the trial population are summarized in Table 3.

Table 3. Baseline Characteristics of Patients Included in CARDINAL

Parameter	**Statistic**	**Enjaymo (N=24)**
Age	Mean (SD) Range	71.3 (8.2) 55 to 85 years
Sex Female Male	n (%)	 15 (63) 9 (38)
Body weight	Mean (SD) Range	67.8 (15.8) 40 to 112 kg
Hemoglobin	Mean (SD), g/dL	8.6 (1.16)
Bilirubin (total)[a]	Mean (SD) mg/dL	3.1 (1.41) (2.6 X ULN)

LDH	Mean (SD), U/L	438 (484.60)
Blood transfusion Within last 6 months Within last 12 months	Median number of transfusions (range)	 2.0 (1, 19) 2.0 (1, 23)

[a] N=21 for bilirubin data excluding patients with Gilbert's syndrome.
LDH: lactate dehydrogenase; kg: kilogram; g/dL: grams per deciliter; mg/dL: milligrams per deciliter; SD: standard deviation; ULN: upper limit of normal.
Efficacy was based on the proportion of patients who met the following criteria: an increase from baseline in Hgb level ≥2 g/dL or a Hgb level ≥12 g/dL at the treatment assessment time point (mean value from Weeks 23, 25, and 26), no blood transfusion from Week 5 through Week 26, and no treatment for CAD beyond what was permitted per protocol from Week 5 through Week 26.

Efficacy of Enjaymo in patients with CAD is described in Table 4.

Table 4. Efficacy Results in Patients with CAD in CARDINAL Part A Study

Parameter	**Statistic**	**Enjaymo N=24**
Responder[a]	n (%)	13 (54)
Hemoglobin level ≥12 g/dL or Increase in Hemoglobin level of ≥2 g/dL	n (%)	15 (63)
Hemoglobin level ≥12 g/dL	n (%)	9 (38)
Increase in Hemoglobin level of ≥2 g/dL	n (%)	15 (63)
Patients not receiving RBC transfusion from Week 5 through Week 26 (transfusion avoidance)	n (%)	17 (71)
Patients not receiving protocol-prohibited CAD medications[b] from Week 5 through Week 26	n (%)	22 (92)

[a] A responder was defined as a patient with an increase from baseline in Hgb level ≥2 g/dL or a Hgb level ≥12 g/dL at the treatment assessment time point (mean value from Weeks 23, 25, and 26), no blood transfusion from Week 5 through Week 26, and no treatment for CAD beyond what was permitted per protocol from Week 5 through Week 26.
[b] Prohibited therapies included rituximab alone or in combination with cytotoxic agents.
CAD: cold agglutinin disease; g/dL: grams per deciliter; RBC: red blood cell.

In Part A, among 14 patients with baseline and follow-up bilirubin values, the mean was 3.23 mg/dL (2.7-fold upper limit of normal [ULN]) at baseline and 0.91 mg/dL (0.8-fold ULN) at the treatment assessment time point. The least-squares (LS) mean change was reduction of -2.23 mg/dL (95% CI: -2.49 to -1.98). Among 17 patients with baseline and follow-up LDH values, the mean LDH was 424 U/L (1.7-fold ULN) at baseline and 301 U/L (1.2-fold ULN) at

the follow-up time point. The least squared mean change in LDH at the treatment assessment time point was reduction of -126 (95% CI: -218 to -35).

In CARDINAL, an increase in mean hemoglobin level of 2.29 g/dL (SE: 0.308) was observed at Week 3 and 3.18 g/dL (SE: 0.476) at treatment assessment time point. The observed model mean change in hemoglobin level from baseline at treatment assessment time point was an improvement of 2.60 g/dL (95% CI: 0.74, 4.46).

In Part B, mean hemoglobin levels were maintained at >10 g/dL. Sustained normalization of mean bilirubin levels was also observed indicating a sustained decrease in hemolysis. Mean hemoglobin level of 12.23 g/dL (range: 9.20–14.40) and 0.96 mg/dL (range: 0.4–1.7) for bilirubin was observed at the last on-treatment visit.

After the last dose of Enjaymo in the study, signs and symptoms of recurrent hemolysis were observed, nine weeks after the last dose in Part B; mean hemoglobin decreased by 2.28 g/dL (SE: 0.402) and mean bilirubin increased by 1.42 mg/dL (SE: 0.192) from the last available values during treatment.

Summary of Evidence
Based on the studies provided to the U.S. Food and Drug Administration, Sutimlimab-jome (Enjaymo) may be considered medically necessary for the treatment of hemolysis in adults when the individual meets the clinical criteria. Sutimlimab-jome (Enjaymo) is considered experimental, investigational and/or unproven for all other non-approved U. S. Food and Drug Administration indications.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J1302

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Label:

1. FDA. Highlights of prescribing information Enjaymo (sutimlimab-jome). U.S. Food and Drug Administration (2/2024). Available at: accessdata.fda.gov (accessed October 6, 2025).

Other:

2. National Organization of Rare Disorders. Cold Agglutinin Disease. Updated September 9, 2024. Available at: rarediseases.org (accessed October 6, 2025).
3. Berentsen S, Brugnara C. Cold Agglutinin Disease. In: UpToDate, Brodsky RA (Ed), UpToDate. Waltham, MA: UpToDate Inc. Available at uptodate.com (access October 6, 2025).

Centers for Medicare & Medicaid Services

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare & Medicaid Services does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at cms.hhs.gov.

Policy History/Revision

Date	Description of Change
5/7/2026	New medical document. Sutimlimab-jome (Enjaymo) may be considered medically necessary for the treatment of hemolysis in adults when the individual meets the clinical criteria. Sutimlimab-jome (Enjaymo) is considered experimental, investigational and/or unproven for all other non-approved U.S. Food and Drug Administration indications.