Sutimlimab-jome (ENJAYMO)
National Drug Monograph
August 2022

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Sutimlimab-jome is a humanized IgG monoclonal antibody that inhibits classical complement. It binds to the classical complement pathway and binds to complement protein component 1, s subcomponent (C1s), a serine protease which cleaves C4. It does not inhibit complement alternative pathways. Inhibition of C1s prevents deposition of complement opsonins on the surface of red blood cells and inhibits hemolysis in patients with Cold Agglutinin Disease (CAD).

Indication(s) Under Review in This Document

- A classical complement inhibitor indicated to decrease the need for red blood cell (RBC) transfusions due to hemolysis with CAD.

Dosage Form(s) Under Review

- Injection, 1,100 mg/22mL (50 mg/mL)

Clinical Evidence Summary

Efficacy Considerations

- Pivotal trial (CARDINAL) was an open-label, single arm trial in patients with CAD who required recent transfusion with a composite endpoint showing improvement in hemoglobin, absence of RBC transfusions, and improvement in fatigue scores through week 26.
- After FDA approval, the phase 3 CRADENZA trial was published comparing sutimlimab-jome to placebo in patients with CAD who did not require a recent transfusion. Again, a composite endpoint was utilized. Sutimlimab-jome again showed improvement in hemoglobin, absence of RBC transfusions, and improvement in fatigue scores through week 26 compared to placebo.
- Efficacy data are summarized in Table 1

Table 1: Efficacy results from clinical trials

Study	Study Design	ECOG PS	Treatment	Results (part A; N=24)
Roth, et al CARDINAL[1]	• OL, Single-group, 6 month	N/A	Sutimlimab over 1 hour	**Primary outcome: composite of normalization of hemoglobin to ≥12 g/dL or an increase in**

	Exclusion: • Cold agglutinin syndrome • Systemic lupus/other autoimmune disease • Overt malignancy • Rituximab within 3 months or rituximab plus chemo within 6 months • Clinically relevant infection within 1 month (e.g. active hepatitis C, pneumonia) • Concurrent corticosteroid unless stable daily dose equivalent ≤10 mg/d prednisone • Pregnancy/lactating **Inclusion:** • Cold agglutinin disease and recent history (w/i 6 mos) of RBC transfusion • Hemoglobin ≤10 g/dL • T. Bili above normal range • 1 or more symptoms of cold agglutinin disorders (i.e. symptomatic anemia, acrocyanosis, Raynaud's phenomenon, hemoglobinuria, disabling circulatory symptoms, major adverse vascular event w/i 3 months)		weekly for 2 weeks then every 2 weeks for up to 6 months Dose: <75 kg 6500 mg ≥75 kg 7500 mg	**hemoglobin of 2 g or more per dL from baseline without RBC transfusion weeks 5-26.** Composite End Point: 54% (95%CI 33-74) N=11 did not meet composite criteria but had evidence of treatment effect (increased hemoglobin, decreased transfusions, or both)
Roth, et al. CADENZA[2]	• Phase 3, PC, DB, 26-week study with an OL extension **EXCLUSIONS:** • CAS secondary to infection, rheumatologic disease, active hematologic malignancy • h/o blood transfusion w/i 6 months or h/o >1 blood transfusion w/i 12 months	N/A	Sutimlimab over 1 hour weekly for 2 weeks then every 2 weeks for up to 6 months Dose: <75 kg 6500 mg ≥75 kg	**Primary Endpoint: composite of Hgb increase from baseline of ≥1.5 g/dL at weeks 23, 25, 26, and absence of blood transfusions from week 5-26 and avoidance of protocol-prohibited CAD medications from week 5-26** 72.7% (n=16) sutimilab versus 15% placebo met criteria for composite primary endpoint. Odds Ratio: 15.9 (95%CI 2.9-88.0) N=3 sutimlimab patients did not meet full response criteria either due to Hgb increase or need for a transfusion

	• systemic lupus or other autoimmune disorder • erythropoietin deficiency • any clinically relevant infection • recent rituximab (w/i 3 mos) or rituximab combination (w/i 6 mos) • concurrent treatment with corticosteroids other than stable dose equivalent to 10mg prednisone **Inclusions:** • Confirmed CAD diagnosis • Hgb ≤10 g/dL • Total bili > normal reference range • Ferritin level above the lower limit of normal • One or more of the following: symptomatic anemia, acrocyanosis, Raynaud's phenomenon, hemoglobinuria, disabling circulatory symptoms and/or major adverse vascular event including thrombosis • Documented vaccinations against encapsulated bacterial pathogens within 5 years of enrollment		7500 mg Sutimlimab N=22 Placebo N=20	

OL=open label; w/i=within; mos=months; RCI=red blood cell; PC=placebo controlled; DB=double-blind; CAS=cold agglutinin syndrome;

- CARDINAL Trial
- Purpose: To assess the efficacy and safety of sutimlimab in patients with cold agglutinin disease and a recent history of transfusion. This was a prospective, open-label, single-group study of a 26-week study period. After the 26 weeks, patients were eligible to continue on an open-label extension study.
- Prior therapies included: corticosteroids, ibrutinib, rituximab, bendamustine/rituximab, fludarabine/rituximab, CHOP-R, CVP, other combination regimens, bortezomib, cyclophosphamide, and plasmapheresis.
- Intervention: Sutimlimab Day 0 and 7, then every 2 weeks up to 26 weeks.
    - Dose: <75 kg: 6500 mg in 500mL over 1 hour
    - Dose: ≥75 kg: 7500 mg in 500 mL over 1 hour

  - Allow infusion over 2 hours if patient has underlying cardiopulmonary disease
- Outcomes
  - Primary Composite: No RBC blood transfusion weeks 5-26 and an increase in hemoglobin to ≥12 g/dL weeks 23, 25, 26 OR Hemoglobin increase ≥2 g/dL from baseline weeks 23, 25, 26
    - N=11 did not meet prespecified criteria for composite endpoint; n=6 had evidence of treatment response (increase in hemoglobin or absence of transfusion or both)
    - N=3 had no evidence of hematologic response
    - N=17 (71%) remained transfusion-free weeks 5-26.
  - Key Secondary:
    - Mean change in hemoglobin from baseline
    - Rate of hemolysis determined by total bilirubin level and LDH (weeks 23, 25, 26)
    - Quality of life assessed by Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale
    - Transfusions weeks 0-5.
- Secondary results:
  - Hemoglobin: least square mean increase of 2.6 g/dL. Mean hemoglobin level at more than 11 g/dL maintained weeks 3-26.
  - Total bili: least square mean decrease of 2.2 mg/dL; mean upper bilirubin upper level below upper limit for duration of treatment.
  - LDH: decrease by at least 1.5 x upper limit of normal at assessment in 58%.
  - Fatigue: mean baseline score 32.5; mean score at assessment 44.3 (higher=less fatigue)
  - Treatment adherence (# doses prescribed divided by # of prespecified doses): 99.7%

- CADENZA Trial
- Purpose: first randomized, placebo-controlled trial of sutimlimab in patients with CAD without a history of recent blood transfusion.
- Confirmed CAD diagnosis
  - Presence of chronic hemolysis
  - Positive polyspecific direct antiglobulin test
  - Monospecific direct antiglobulin test strongly positive for C3d
  - IgG direct antiglobulin tests ≤1+
  - Cold agglutinin titer ≥64 at 4◦C
  - No evidence of overt malignant disease
- Intervention: Sutimlimab Day 0 and 7, then every 2 weeks up to 26 weeks.
  - Dose: <75 kg: 6500 mg in 500mL over 1 hour
  - Dose: ≥75 kg: 7500 mg in 500 mL over 1 hour
  - Allow infusion over 2 hours if patient has underlying cardiopulmonary disease
- Outcomes:
  - Primary Composite Endpoint
    - Sutimlimab resulted in rapid and sustained increase in Hgb levels with no meaningful change in placebo patients

    - Key Secondary
        - Hgb change from baseline at weeks 23, 25, 26
        - Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale (higher score=less fatigue; increase ≥5 points clinically significant)
        - Change from baseline for total bili, LDH, haptoglobin, reticulocytes
        - Mean increase of ≥1 g/dL, ≥1.5 g/dL, ≥2 g/dL, and ≥3 g/dL in Hgb levels
        - Pharmacodynamic endpoints: changes in complement pathway activity
- Secondary Results
    - Hemolysis: sutimlimab led to rapid and sustained control of hemolysis throughout study based on mean total bili and LDH levels. Increase in haptoglobin level corresponded to decrease in total bili but no change occurred in the placebo arm
    - Fatigue: rapid and sustained improvement in FACIT-Fatigue Score for sutimlimab with clinically meaningful changes by week 1 versus no change for placebo patients

Safety Considerations

Safety Results from Clinical Trials:

- CARDINAL
- Majority of adverse events were grade 1 or 2
- No serious infections were related to sutimlimab infusions
- No evidence of systemic lupus or other autoimmune disease
- No thromboembolism during study, but 58% received antithrombotic medications which were mostly ongoing prior to study enrollment.
- CRADENZA
- Majority of adverse events were lower grades.
- Three patients discontinued sutimlimab-jome due to adverse events.

Table 2: Safety results from clinical trials [3]

Study	Results
CARDINAL	**Any AE:** n=124 **Serious adverse events:** N=27 (29%) **Serious infections:** n=2 (8%) **AEs leading to discontinuation:** 0 **Deaths due to AE** N=1
CREDENZA	**Any AE:** 96% vs 100% **Serious adverse events:** N=3 (14%) **Serious infections:** N=3 (14%) **AEs leading to discontinuation:** N=3 (14%) **Deaths due to AE:** 0

- **Boxed warnings:** None

- **Contraindications:** known hypersensitivity to sutimlimab-jome or any of the inactive ingredients
- **Other warnings / precautions**:
    - **Serious infections**: therapy may increase susceptibility to infections caused by encapsulated bacteria (e.g. Neisseria meningitides, Streptococcus pneumoniae, H. influenzae). Vaccinate/revaccinated for encapsulated organisms according to the most recent ACIP recommendations for patients with persistent complement deficiencies. Vaccinate 2 weeks prior to the first sutimlimab-jome infusion unless urgent sutimlimab-jome is needed in an unvaccinated patient; them vaccinate as soon as possible. Serious infections (bacterial and viral) were reported in 17% of patients. For current active systemic reactions, monitor and consider dose interruption. Sutimlimab-jome was not studied in patients with chronic systemic infections like hepatitis B, hepatitis C, or HIV.
    - **Infusion-related reactions:** 8% in Cardinal study (shortness of breath, rapid heartbeat, nausea, flushing, headache). If reaction occurs, interrupt infusions. Discontinue therapy and provide supportive care if signs of hypersensitivity reaction (cardiovascular instability, respiratory compromise).
    - **Risk of autoimmune disease:** Based on mechanism of action, sutimlimab-jome may increase risk for autoimmune diseases such as systemic lupus erythrematosus.
    - **Recurrent hemolysis after discontinuation:** Following treatment interruption, monitor for signs/symptoms of recurrent hemolysis (↑t. bili or LDH, ↓Hgb), reappearance of symptoms like fatigue, dyspnea, palpitations, or hemoglobinuria. Consider restarting sutimlimab-jome if signs if recurrent hemolysis occur after discontinuation.
- **Adverse reactions**
    - **Common**: Infections in 54% (gastroenteritis, nasopharyngitis, upper respiratory tract), GI disorders in 33%, General/Administration site: 29%
    - **Serious Adverse events / Deaths / Discontinuation:** No serious adverse events were due to sutimlimab. No discontinuation of therapy due to adverse events. 1 death unrelated to sutimlimab.

Other Therapeutic Options

Alternative treatments for cold-agglutinin disease are listed in table 3 below

Table 3 Treatment Alternatives

Drug	Formulary status	Clinical Guidance	Other Considerations
Sutimlimab-jome	TBD	FDA indication: Classical complement inhibitor to decrease the need for RBC transfusion due to hemolysis with CAD	Infusion given for weekly x2 then every 2 weeks for 26 weeks Low rate of serious adverse events
Rituximab[4,5]	F	No FDA indication Weekly doses for 4 weeks: ORR 45-58% (mostly PR); sustained remission unlikely	Responses were a composite of signs, symptoms, anemia, monoclonal serum protein
Rituximab + bendamustine[6]	R=F B=NF	No FDA indication R day 1 + B D1,2; 4 cycles at 28-day intervals ORR: 71% (40% CR) Majority had sustained remission	Risk for neutropenia
Bortezomib[7]	F	No FDA indication Short course single course 1.3 mg/m2 D 1, 4, 8 11 CR=15.8%; PR=15.8%	Refractory or relapsed disease Treatment-related adverse events (including neuropathy) rare; 1 grade 3-4 event due to bortezomib

RCB=red blood cell; CAD=cold agglutinin disease; PR=partial response; CR=complete response;

Projected Place in Therapy [8,9]

- Immune-mediated hemolytic anemia is divided into 2 separate types: warm antibody type and cold antibody type. Cold Agglutinin Disease (CAD) is much less common than warm autoimmune hemolytic anemia.
- CAD is a form of hemolytic anemia in which cold agglutinins (B-cell derived IgM autoantibodies) recognize and bind to antigens on red blood cells at temperatures below normal body temperature. Binding leads to activation of the complement cascade and results in clinical symptoms related to agglutination in colder parts of the body. The result is extravascular hemolytic anemia, generally without other typical features of warm hemolytic anemia.
- CAD induced symptoms include:
    - Acrocyanosis (fingertips, toes, nose, ears)
    - Livedo reticularis (patchy, reticulated pattern on the skin)
    - Raynaud phenomena (demarcated color changes of skin on digits)
    - Cutaneous ulcerations/necrosis
    - Pain on swallowing cold food or liquids
    - Hemolytic anemia (Hgb 9-10 g/dL)
    - Fatigue
    - Venous thromboembolism
- CAD diagnosis in VA: From FY21Q3-FY22Q2 N=183 patients with a diagnosis
- PADR: since launch in Feb 2022: 2 PADR with 100% approval
- Treatment: Previously, no drugs were FDA approved to treat CAD. CAD typically does not respond well to drug therapy used for warm agglutinin disease like corticosteroids.
- Therapies
    - Avoid cold temperatures
    - Transfusions
    - Treatment of any underlying disorders (secondary CAD)
    - Therapy targeting b-cell clone producing immunoglobulins
        - Rituximab plus bendamustine
        - Rituximab single agent (depletes B-cells)
        - Bortezomib
- Sutimlimab-jome is the first drug to receive an FDA indication for CAD. The indication was based on an open-label, single-arm trial in 24 patients with CAD receiving transfusions (CARDINAL). The composite endpoint of increase in hemoglobin and no transfusions was met in 54% of patients with sustained responses. Secondary outcomes included a decrease in hemolysis and improvement in fatigue scores.
- Recently, a phase 3 study, CRADENZA, studied sutimlimab-jome versus placebo for patients with CAD but without recent transfusion. A similarly high composite endpoint with sustained response was seen.
- Compliment-directed therapies are likely needed to be given for a lifetime or until disease progression.

- Other therapies used for CAD include single-agent rituximab (but remission is not maintained and no FDA indication), rituximab plus bendamustine (high complete response rate, response appears maintained, no FDA indication), or bortezomib (short course of therapy, studied in refractory patients and lower complete response than rituximab plus bendamustine, duration of response maintained for at least 16 months).
- Due to the rarity of this diagnosis, it is unlikely any of the alternative therapies will be compared to sutimlimab-jome. Consider beginning with a B-cell directed therapy (rituximab or bendamustine/rituximab) if the patient is fit for immunochemotherapy, as these can be given for short courses (generally 4 courses) with some sustained activity and can be repeated if needed. These can be followed by compliment-directed therapy with sutimlimab-jome.
- Given the data, FDA indication, sustained response, and rarity of the disease, sutimlimab-jome should be available for the rare VA patients with chronic cold agglutinin disease.

References

[1] Roth A, Barchellini W, D'Sa S, Miyakawa Y, Broome CM, et al. Sutimlimab in cold agglutinin disease. New Eng J Med 2021;384:1323-34.
[2] Roth A, Berentsen S, Barchellini W, D'Sa S, Jilma B, et al. Sutimlimab in patients with cold agglutinin disease: Results of the randomized placebo-controlled phase 3 CADENZA trial. Blood 2022; doi: 10.1182/blood.2021014955 (on-line ahead of print)
[3] ENJAYMO (sutimlimab-jome) Product Package Insert. Biovertiv USA Inc. A Sanofi Company. Waltham, MA. 2022.
[4] Berentsen S, Ulvestad E, Gjertsen BT, Hjorth-Hansen H, Langholm R, et al. Rituximab for primary chronic cold agglutinin disease: a prospective study of 37 courses of therapy in 27 patients. Blood 2004; 103:2925-2928.
[5] Swiecicki PL, Hegerova LT, Gertz MA. Cold agglutinin disease. Blood 2013; 122:1114-1121.
[6] Berentsen S, Randen U, Oksman M, Birgens H, Andersen Tvedt TH, et al. Bendamustine plus rituximab for chronic cold agglutinin disease: results of a Nordic prospective multicenter trial. Blood 2017; 130:537-541.
[7] Rossi G, Gramegna D, Paoloni F, Fattizzo B, Binda F, et al. Short course of bortezomib in anemic patients with relapsed cold agglutinin disease: a phase 2 prospective GIMEMA study. Blood 2018; 132: 547-550.
[8] Gertz MA. Updates on the diagnosis and management of cold autoimmune hemolytic anemia. Hematol Oncol Clin N Am 2022; 36:341-352.
[9] Barchellini W, Zaninoni A, Gianotta JA, Fattizzo B. New Insights in autoimmune hemolytic anemia: From Pathogenesis to Therapy. J Clin Med 2020; 9: doi:10.3390/jcm9123859.

Prepared August 2022. Contact person: Mark C. Geraci, Pharm.D., BCOP, National PBM Clinical Pharmacy Program Manager, Formulary management, VA Pharmacy Benefits Management Services (10P4P)

Appendix A. Acquisition Prices and Cost Considerations

Refer to VA pricing resources for updated information