New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Enjaymo™ (sutimlimab-jome) [Bioverativ USA, Inc.]**
Dosage Formulations:	Intravenous injection: 1100 mg/22 mL single-dose vial
FDA Approval Date: **FDB File Date:**	FDA: February 4, 2022 FDB: February 13, 2022
Indication:	To decrease the need for red blood cell (RBC) transfusion due to hemolysis in adults with cold agglutinin disease (CAD).
Mechanism of Action:	Sutimlimab-jome is an immunoglobulin G (IgG), subclass 4 (IgG4) monoclonal antibody (mAb) that inhibits the classical complement pathway (CP) and specifically binds to complement protein component 1, s subcomponent (C1s), a serine protease which cleaves complement protein component 4 (C4). Sutimlimab-jome does not inhibit the lectin and alternative pathways. Inhibition of the classical complement pathway at the level of C1s prevents deposition of complement opsonins on the surface of RBCs, resulting in inhibition of hemolysis in patients with CAD.
Dose/ Administration:	Enjaymo dosing is based on body weight. For patients weighing between 39 and 75 kg, the recommended dose is 6,500 mg and for patients weighing 75 kg or more the recommended dose is 7,500 mg. Administer Enjaymo intravenously weekly for the first two weeks, then administer every two weeks thereafter. If a dose is missed, administer as soon as possible. If the duration after the last dose exceeds 17 days, administer Enjaymo weekly for two weeks, then continue every two-week dosing thereafter.

Disease State Clinical Highlights:	• CAD is a form of autoimmune hemolytic anemia (AIHA), characterized by premature destruction of red blood cells (hemolysis). CAD accounts for about 15% of the AIHAs.
	• Cold agglutinins (CAs) are predominately IgM autoantibodies that are directed against RBC antigens. The optimum temperature for CAs is 3 to 4 degrees Celsius or 37 to 39 degrees Fahrenheit. When exposed to temperatures below normal core body temperature, CAs bind to antigens on the surface of RBCs primarily in the peripheral areas of the body and cause agglutination (clumping) of RBCs. Once bound, IgM recruits components of the complement eventually leading to the RBC being coated with C3b (an important component of the innate immune system). C3b-coated RBCs undergo phagocytosis by macrophages resulting in hemolytic anemia. On the remaining RBCs, IgM dissociates upon warming leaving C3b attached. C3b undergoes cleavage to C3d, which can be detected by the direct antiglobulin test (DAT) used for CAD diagnosis. DAT tests determine whether RBCs have antibodies attached to their surface. The DAT test used for diagnosis in CAD in the Coombs test, which detects complement component C3d.
	• CAD is an extremely rare disease, with a prevalence of about 16 people per million. It normally affects patients aged 40 to 80 years with a median age at symptom onset of 65 years. The five-year survival rate is approximately 83%, with infection being the most common cause of death.
	• CAD can be classified as either primary (unknown cause), secondary (due to another condition such as infection), or immunoproliferative disease (e.g., non-Hodgkin's lymphoma, chronic lymphocytic leukemia).
	• According to a study involving 232 individuals diagnosed with CAD, the most common clinical manifestations were:
	  ○ Anemia (median hemoglobin 9.5 g/dL): 90%
	  ○ Hemolytic marker (high lactate dehydrogenase [LDH] and bilirubin): 90%
	  ○ Cold-induced symptoms (e.g., acrocyanosis, Raynaud phenomenon): 52%
	• Diagnosis of CAD involves documentation of the following:

	○ Evidence of hemolysis ○ Positive direct antiglobulin (Coombs) test for C3d only ○ Cold agglutinin titer of ≥ 64 at 4 degrees Celsius ○ Lack of overt malignant disease
Drug Clinical Highlights:	• Enjaymo was FDA-approved under priority review, and previously received Breakthrough Therapy and Orphan Drug designations. It is the first drug approved to reduce the need for red blood cell transfusion in adults with CAD-mediated hemolysis. <u>Warnings/Precautions:</u> • Serious Infections ○ Enjaymo may increase susceptibility to serious infections including those caused by encapsulated bacteria such as *Neisseria meningitides* (any serogroup), *Streptococcus pneumoniae*, and *Haemophilus influenzae.* Serious infections (bacterial and viral) were reported in 17% (4/24) patients receiving Enjaymo (including sepsis, respiratory, and skin infections). ○ Vaccinate patients for encapsulated bacteria according to the most recent ACIP recommendations. Immunize patients without vaccination history at least two weeks prior to receiving first dose of Enjaymo. • Infusion-Related Reactions ○ Enjaymo is contraindicated in patients with known hypersensitivity reactions to sutimlimab-jome or any of the inactive ingredients. Administration may result in infusion-related reactions, 8% (2/24) of patients treated with Enjaymo experienced infusion-related reactions. ○ Monitor patients for infusion-related reactions and discontinue infusion and institute appropriate supportive measures if signs of hypersensitivity reactions occur. • Risk of Autoimmune Disease ○ Based on its mechanism of action, Enjaymo may potentially increase the risk for developing autoimmune diseases such as systemic lupus erythematosus (SLE). Monitor patients treated with Enjaymo for signs and symptoms and manage medically if symptoms occur. • Recurrent Hemolysis after Enjaymo Discontinuation ○ If treatment with Enjaymo is interrupted/discontinued, closely monitor patients for signs and symptoms of recurrent hemolysis. Consider restarting Enjaymo if hemolysis recurs while off therapy. <u>Pregnancy/Lactation:</u> • There are no data available on Enjaymo use in pregnant women. Human IgG antibodies are known to cross the placental barrier, therefore Enjaymo may be transmitted from the mother to the developing fetus. <u>Clinical Study</u> • CARDINAL (n = 24) (NCT03347396): open-label, single-arm, 6-month trial involving 24 patients. Following the completion of the 6-month treatment period, patients continued to receive Enjaymo in a long-term safety and durability of response extension phase for an additional 24 months. ○ Key Inclusion Criteria: ▪ Body weight ≥ 39 kg at screening ▪ Confirmed diagnosis of CAD based on: • Chronic hemolysis • Polyspecific direct antiglobulin test (DAT) positive • Monospecific DAT strongly positive for C3d • Cold agglutinin titer ≥ 64 at 4 degrees Celsius • Immunoglobulin G (IgG) DAT ≤ 1+ • No overt malignant disease

- History of at least one documented blood transfusion within 6 months of enrollment
- Hemoglobin (Hgb) level ≤ 10 g/dL
- Bilirubin level above the normal reference range

- Key Exclusion Criteria:
  - Cold agglutinin secondary to infection, rheumatologic disease, or active hematologic malignancy
  - Clinically relevant infection of any kind within month preceding enrollment
  - Clinical diagnosis of SLE
  - Positive hepatitis panel
  - Treatment with rituximab monotherapy within 3 months or rituximab combination therapy within 6 months prior to enrollment
- Baseline Characteristics
  - Mean age: 71.3 years (range 55 to 85)
  - Mean body weight: 67.8 kg (range 40 to 112)
  - Mean Hgb: 8.6 g/dL
  - Mean bilirubin: 3.1 mg/dL
  - Mean LDH: 438 U/L
- Primary Outcome Measure
  - Study participants were administered 6.5 g or 7.5 g of Enjaymo (based on body weight) intravenously over approximately 60 minutes on Day 0, Day 7, and every 14 days thereafter through Week 25.
  - 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
    - No treatment for CAD beyond what was permitted per protocol from Week 5 through Week 26.

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

*Responder defined as a patient who met all of the primary outcome measure criteria.

- Secondary endpoints
  - Mean change from baseline in Hgb level up to Week 26: the least-square mean increase in Hgb, calculated with the use of a mixed model for repeated measures, was 2.6 g/dL.
  - Mean change from baseline in bilirubin up to Week 26: among the 14 patients with baseline and follow-up bilirubin values, the mean was 3.23 mg/dL at baseline and 0.91 mg/dL at the treatment assessment time point.
  - Mean change from baseline in LDH up to Week 26: among the 17 patients with baselines and follow-up LDH values, the mean LDH was 424 U/L at baseline and 301 U/L at the follow-up time point.

- Adverse Reactions: 7 patients reported at least one serious adverse event, none of which were determined to be caused by the study drug. Adverse events reported in ≥ 5% of patient receiving Enjaymo are listed below.

Adverse Reaction	n (%) N=24
Infections	
Respiratory tract infection	6 (25)
Viral infection	3 (13)
Urinary tract infection	2 (8)
Bacterial infection	2 (8)
Vascular disorders	
Cyanosis	2 (8)
Systemic hypertension	2 (8)
Gastrointestinal disorders	
Diarrhea	3 (13)
Dyspepsia	3 (13)
Gastroenteritis	2 (8)
Abdominal pain	2 (8)
Respiratory, thoracic, and mediastinal disorders	
Cough	3 (13)
Musculoskeletal and connective tissue disorders	
Arthralgia, arthritis	3 (13)
General disorders and administration site conditions	
Peripheral edema	3 (13)
Fatigue	2 (8)
Infusion reaction	2 (8)
Nervous system disorders	
Headache	2 (8)

Price Per Unit (WAC):

$1,800.00 per vial

Annual cost for maintenance dosing (39 to 75 kg): $280,800.00
Annual cost for maintenance dosing (75 kg and up): $327,600.00

Therapeutic Alternatives:

- Treatment of CAD is dependent upon the severity of clinical manifestations. Cold avoidance, particularly head, face, and extremities, is used to control cold-induced symptoms and hemolysis. Around 25% of CAD patients will use supportive measures such as cold avoidance to manage their disease.
- Blood transfusions, plasmapheresis, and treatment with intravenous immunoglobulins (IVIG) are used when patients present with severe, urgent hemolysis. Blood transfusions are more often needed in winter months and in colder climates.
- For symptomatic primary CAD patients, treatment is indicated for those experiencing symptomatic anemia and cold-induced ischemic symptoms interfering with activities of daily living. Rituximab is the treatment of choice, either as monotherapy or in combination with chemotherapy agents in patients who are able to tolerate chemotherapy. Bendamustine and fludarabine are the two most common agents used along with rituximab, however fludarabine is more toxic and is considered a third-line therapy in eligible patients.
- Responses to rituximab-based regimens can be delayed by several months. In prospective, nonrandomized studies response rates for rituximab monotherapy have ranged from 45-54% with response durations ranging from 6.5 to 11 months. In retrospective studies response rates have been as high as 83%. In a prospective study involving 45 patients treated with rituximab plus bendamustine, responses were seen in 32 (71%) of patients, and only 3 patients relapsed after 32 months.

Regimen	Dosing	Number of Infusions, Cycles	Cost (WAC)
Enjaymo	7,500 mg every 2 weeks	1 infusion every 2 weeks	$327,600 per year
Rituximab	375 mg/m^2 once weekly	1 infusion weekly for 4 weeks	$30,065 per cycle
Rituximab/ Bendamustine combination	375 mg/m^2 on Day 1 90 mg/m^2 on Days 1 and 2	Four 28-day cycles	$69,645 per 4 cycles

*estimates based on 75kg patient

Prior Authorization Approval Criteria:

Must meet the following criteria:

Initial Therapy

- Prescribed by or in consultation with an appropriate specialist in the treated disease state **AND**
- Participant is aged at least 18 years **AND**
- Documented diagnosis of primary CAD (D59.12) confirmed by:
  - Evidence of hemolysis **AND**
  - Positive direct antiglobulin (Coombs) test for C3d only **AND**
  - Cold agglutinin titer of ≥ 64 at 4 degrees Celsius **AND**
  - Lack of overt malignant disease **AND**
- Documented history of at least one blood transfusion in the past 6 months **AND**
- Hemoglobin level ≤ 10.0 g/dL **AND**
- Bilirubin level above normal reference range, including patients with Gilbert's syndrome **AND**
- Presence of one or more symptoms associated with CAD:
  - Symptomatic anemia
  - Acrocyanosis
  - Raynaud's phenomenon
  - Hemoglobinuria
  - Disabling circulatory symptoms
  - Major adverse vascular event **AND**
- Participant not eligible for rituximab-based therapy due to one of the following:
  - Unresponsive to previous rituximab-based therapy **OR**
  - Documented medical reason why rituximab-based therapy is not appropriate or is contraindicated
- Initial approval for 6 months

Continuation of Therapy

- Documentation of benefit from therapy including one of the following:
  - Increase in Hgb from baseline by ≥ 2 g/dL or achieving Hgb level of ≥ 12 g/dL
  - Normalization of LDH and/or bilirubin levels
  - Decrease in transfusion burden
- Continued approval for 12 months

Additional Provider Diagnostic/Monitoring Criteria, if desired:

- Participant (female of appropriate age) is utilizing concurrent birth control methods

	• Vaccinate patients for encapsulated bacteria according to the most recent ACIP recommendations. Immunize patients without vaccination history at least two weeks prior to receiving first dose of Enjaymo.
Implication to State Medicaid Program:	• Empaveli® (pegcetacoplan) is a C3 complement inhibitor FDA-approved for paroxysmal nocturnal hemoglobinuria (PNH). It is currently in a Phase III trial for CAD with an estimated completion in 2024. • Iptacopan is another C3 complement inhibitor currently in a Phase II trial for CAD. Results are expected in 2025. • Agents that target C5 (Ultomiris® and Soliris®) would not be expected to lessen hemolysis in CAD patients and are not currently in trials for CAD. • Enjaymo is not currently in development for other indications.

References:

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