Policy Number	**RX501.193**
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Narsoplimab-wuug

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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 (FDA) 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

Narsoplimab-wuug (Yartemlea®) **may be considered medically necessary** for the treatment of hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA) when all the following criteria are met:

1. Individual is 2 years of age or older;
2. Individual has hematopoietic stem cell transplant-associated thrombotic microangiopathy diagnosis confirmed by:
   a. Renal biopsy; OR
   b. 4 or more of the following:
      i. Schistocytes;
      ii. Thrombocytopenia: 50% or greater reduction from baseline after engraftment or transfusion dependent;
      iii. Anemia: 1 g/dL reduction in hemoglobin (Hb) from baseline after engraftment or transfusion dependence;
      iv. Lactate dehydrogenase (LDH): > upper normal limit;
      v. Hypertension: >140/90 in individuals 18 years of age or older OR >99th percentile in individuals <18 years of age;
      vi. Proteinuria: spot urine protein creatinine ratio (uPCR) 1 mg/mg or higher;
      vii. Elevated sC5b9: greater than the upper normal limit.

Narsoplimab-wuug (Yartemlea®) **is considered experimental, investigational and/or unproven** for all other non-Food and Drug Administration approved indications.

Policy Guidelines

None.

Description

Allogenic hematopoietic stem cell transplantation (allo-HSCT) remains the only curative option for many malignant and non-malignant diseases. Despite improvement in outcomes, increased morbidity and mortality continue to be a significant issue, including graft-versus-host disease (GVHD), disease relapse, infections, etc. Thrombotic microangiopathy (TMA) following allo-HSCT (also called transplant-associated thrombotic microangiopathy [TA-TMA]) is increasingly being recognized as a significant risk factor for increased morbidity and mortality following allo-HSCT. (3)

TA-TMA is characterized by microangiopathic hemolytic anemia and thrombocytopenia, because of generalized endothelial dysfunction and complement activation, leading to microthrombi formation. It has a very heterogenous clinical picture and may affect any organ of the body but most commonly the kidneys and the brain. Since these features are also shared between other diseases, such as capillary leak syndrome, GvHD, thrombotic thrombocytopenic purpura (TTP), veno-occlusive disease (VOD), etc., the diagnosis of TA-TMA is commonly delayed or masked. This, along with the lack of consensus criteria for TA-TMA diagnosis, results in delayed or inappropriate treatment, leading to the increased morbidity and mortality associated with the syndrome. (3)

The precise incidence of TA-TMA remains largely unknown, varying between 0.5% and 76% in the allo-HSCT setting, whereas its incidence is slightly lower in the autologous setting (0–27%). This is partly due to the lack of a gold standard for its diagnosis, leading to variable definitions of TA-TMA in different centers and studies. TA-TMA is most often described as an early event in allo-HSCT with a time of onset between 32 and 86 days. It is considered one of the most severe complications of allo-HSCT; prognosis is generally poor with a case-fatality varying between 50 and 75%. (3)

Diagnostic Criteria

Diagnosis of TA-TMA is difficult as there is insufficient criteria. sC5b9, the soluble form of the membrane attack complex of the terminal complement pathway, is the most studied prognostic biomarker for the disease, though its sensitivity and specificity remain suboptimal for clinical use. (4)

Table 1 shows the variations in common diagnostic criteria used for TA-TMA diagnosis. (4)

Table 1. Variations in Common Diagnostic Criteria Used for TA-TMA Diagnosis

	BMT-CTN	**IWG**	**Clinical TMA(C-TMA) (Modified Cho)**	**New Consensus TA-TMA[d] (modified Jodele)**
Comment	Meeting all criteria	Meeting all criteria	Biopsy proven disease or meet all criteria concurrently for ≥2 times in 14 days	Biopsy proven disease or meet ≥4 criteria 1-7 concurrently for ≥2 times in 14 days
1) Schistocytes[a]	≥2/HPF	≥4% (8/HPF)	≥2/HPF	Presence
2) Thrombocytopenia		X	X	≥50% Plt reduction from baseline after engraftment or transfusion dependence

3) Anemia		X	X	≥1 g/dL Hb reduction from baseline after engraftment or transfusion dependence (rule out AIHA & PRCA)
4) Elevated LDH	X	X	X[b]	LDH>ULN
5) Hypertension				1. >99th percentile for age (<18 yr) 2. ≥140/90 (≥18 yr)
6) Proteinuria				Spot rUPCR ≥1 mg/mg
7) Elevated sC5b9				sC5b9 > ULN
Low haptoglobin		X		
Negative DAT (Coombs)	X			
Renal or Neurologic dysfunction	X			
Rule out mimics or alternative causes of secondary TMA[c]			- Coagulopathy or DIC - AIHA or PRCA - Overt relapse of malignancy	

AIHA: autoimmune hemolytic anemia; BMT-CTN: Blood and Marrow Transplant Clinical Trials Network; DAT: direct antiglobulin test (direct Coombs); DIC: disseminated intravascular coagulation; Hb: hemoglobin; HPF: high-power field; IWG: International Working Group; LDH: lactate dehydrogenase; Plt: platelet; PRCA: pure red cell aplasia; rUPCR: random urine protein creatine ratio; TA-TMA: transfusion-associated thrombotic microangiopathy; ULN: upper limit of normal; yr: year.

[a] Schistocyte is required in all definitions except the new consensus criteria.

[b] Various adult cohorts have used different LDH thresholds including 1.5x or 2x due to its lack of specificity.

[c] No singular laboratory testing is sufficient for diagnosing mimics or alternative triggers for secondary TMA; clinical diagnosis is required.

[d] High-risk TA-TMA in the new consensus criteria is defined as those meeting standard risk criteria plus any one of the following: sC5b9>ULN, rUPCR≥1 mg/mg, organ dysfunction, LDH ≥2x ULN, concurrent grade 2 to 4 acute graft-versus-host disease, concurrent viral infection.

Representatives from the American Society for Transplantation and Cellular Therapy, Center for International Bone Marrow Transplant Research, Asia-Pacific Blood and Marrow Transplantation, and European Society for Blood and Marrow Transplantation recommended using modified Jodele criteria for diagnosis. (2)

Table 2. TMA Harmonization Panel Consensus Recommended Diagnostic Criteria, Modified Jodele Criteria

Biopsy-proven disease (kidney or GI) or	
Clinical criteria: Must meet ≥4 of the following 7 criteria within 14 days at 2 consecutive time points	
Anemia[a]	Defined as one of the following: 1. Failure to achieve transfusion independence for pRBCs despite evidence of neutrophil engraftment 2. Hemoglobin decline from patient's baseline by 1 g/dL 3. New onset of transfusion dependence Rule out other causes of anemia, such as AIHA and PRCA
Thrombocytopenia[a]	Defined as one of the following: 1. Failure to achieve platelet engraftment 2. Higher than expected platelet transfusion needs 3. Refractoriness to platelet transfusions 4. 50% reduction or greater in baseline platelet count after full platelet engraftment
Elevated LDH	>ULN for age
Schistocytes	Present
Hypertension	>99th percentile for age (<18 yrs), or systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg (≥18 yrs)
Elevated sC5b-9	≥ULN
Proteinuria	≥1 mg/mg rUPCR

AIHA: autoimmune hemolytic anemia; BP: blood pressure; dL: deciliter; g: gram; GI: gastrointestinal; LDH: lactate dehydrogenase; mmHg: millimeter of mercury; mg: milligram; pRBC: packed red blood cells; PRCA: pure red cell aplasia; rUPCR: random urine protein creatine ratio; TMA: thrombotic microangiopathy; ULN: upper limit normal; yrs: years.

This group proposes that patients be routinely screened in the first 100 days post-HCT, with a low threshold for screening beyond this time point when patients have laboratory features of TA-TMA and concurrent complications. Standard screening should include at least weekly complete blood count, LDH, rUPCR, and blood smears for schistocytes. These are nonspecific laboratory markers; however, when they persist without other explanations and occur simultaneously, TA-TMA should be strongly considered, and if ≥3 of 6 screening features are positive (anemia, thrombocytopenia, elevated LDH, schistocytes, refractory hypertension, or proteinuria), additional laboratory workup should be pursued. (2)

Narsoplimab-wuug

Narsoplimab, a mannan-binding lectin-associated serine protease-2 (MASP-2), is an inhibitor of the lectin pathway of the complement cascade. Narsoplimab blocks complement activation and endothelial injury without affecting pathways of innate immunity, sparing the immunologic dysfunction noted with other complement inhibitors (such as eculizumab). (1, 3)

Regulatory Status

The U.S. Food and Drug Administration (FDA) approved narsoplimab-wuug (Yartemlea®, Omeros Corp., Seattle, WA) in December 2025 as a mannan-binding lectin-associated serine protease-2 (MASP-2) inhibitor indicated for the treatment of adult and pediatric patients 2 years of age and older with hematopoietic stem-cell transplant-associated thrombotic microangiopathy (TA-TMA). (1)

Rationale

This policy is based on the U.S. Food and Drug Administration (FDA) labeled indications for narsoplimab-wuug (Yartemlea®) and review of relevant professional guidelines and position statements.

Narsoplimab-wuug (Yartemlea®) (1)
The efficacy of Yartemlea was assessed in (i) a single-arm, open-label study (TA-TMA Study) that enrolled 28 adult patients who developed transplant-associated thrombotic microangiopathy (TA-TMA) following hematopoietic stem-cell transplantation (HCT) and (ii) 19 adult and pediatric patients with TA-TMA with evaluable patient-level response data enrolled in an expanded access program (EAP). In the TA-TMA Study, 24 patients received Yartemlea 4 mg/kg intravenously once weekly, and 4 patients received Yartemlea 370 mg intravenously once weekly. The median number of Yartemlea administrations received by the 28 TA-TMA Study patients plus the 19 EAP patients was 8 (range: 2-34), and the median duration of therapy was 8 weeks (range: 2-16 weeks).

Baseline demographic and disease-related characteristics are shown in Table 3. The TA-TMA Study patients had a confirmed diagnosis of TA-TMA per the diagnostic criteria as follows: platelet count < 150,000/µL, evidence of microangiopathic hemolysis (presence of schistocytes, serum lactate dehydrogenase [LDH] greater than the upper limit of normal [ULN] and/or haptoglobin less than the lower limit of normal [LLN]), and renal dysfunction. Patients in the EAP were similarly thrombocytopenic with evidence of microangiopathic hemolytic anemia.

Table 3. Characteristics of TA-TMA Patients Treated with Yartemlea in the TA-TMA Study and Expanded Access Program (EAP)

Parameter	TA-TMA Study	Expanded Access Program (N=19)[a]	
	Adult (N=28)	Pediatric (n=6)	Adult (n=13)
Median age (years) (range)	48 (22, 68)	10.5 (5, 15)	62 (19, 71)
Race, n (%)[b]			
• White	17 (61)	--	--
• Asian	7 (25)		
• Black or African American	2 (7)		
• Native Hawaiian or Other Pacific Islander	1 (4)		
• Other	1 (4)		

Ethnicity, n (%)[b] • Hispanic or Latino/a • Not Hispanic or Latino/a	 2 (7) 26 (93)	--	--
Gender, n (%) • Male • Female	 20 (71) 8 (29)	 2 (33) 4 (67)	 5 (38) 8 (62)
Elevated LDH ≥2x ULN, n (%)	20 (71)	6 (100)	7 (54)
Grade II-IV acute GVHD, n (%)	19 (68)	5 (83)	11 (85)
Organ dysfunction, n (%)	27 (96)	6 (100)	13 (100)
Renal dysfunction, n (%)	21 (75)	5 (83)	13 (100)
Pulmonary dysfunction, n (%)	5 (18)	0 (0)	2 (15)
Neurological dysfunction, n (%)	16 (57)	2 (33)	4 (31)
Infection, n (%)	24 (86)	6 (100)	8 (62)

GVHD: graft vs host disease; LDH: lactate dehydrogenase; TA-TMA: transplant-associated thrombotic microangiopathy; ULN: upper limits of normal.

[a] Includes patients from EAP with available patient-level data. The entire EAP consisted of 221 patients; patient-level response data were available in 13 adult and 6 pediatric patients.

[b] Race and ethnicity data were not available for the 19 patients in the EAP.

Among patients in the TA-TMA Study, the median time from HCT to TMA diagnosis was 73.5 days (range: 21–436) and the median time from TMA diagnosis to first dose of narsoplimab was 13.5 days (range: 4–196). Among the 19 adult and pediatric patients in the EAP, the median time from HCT to TMA diagnosis was 81 days (range: 24–452) and the median time from TMA diagnosis to first dose of narsoplimab was 3 days (range: 0–52).

The primary efficacy assessment of Yartemlea was based on TMA response defined as improvement in both of two laboratory TMA markers (LDH and platelet counts) and either improvement in organ function or independence from transfusions. The same response criteria were applied to both the TA-TMA Study and EAP patients.

Improvement in platelet count was defined as follows:

- For baseline platelet count ≤ 20,000/µL: (i) ≥ 3-fold increase in platelet count, (ii) post-baseline platelet count > 30,000/µL, and (iii) receipt of no platelet transfusions within 2 days prior to the platelet count assessment.
- For baseline platelet count > 20,000/µL: (i) ≥ 50% increase in platelet count, (ii) platelet count > 75,000/µL, and (iii) receipt of no platelet transfusions within 2 days prior to the platelet count assessment.

To meet LDH improvement criteria, LDH levels were required to be < 1.5x ULN.

In the TA-TMA Study and the EAP, TA-TMA response was achieved in 17/28 (60.7%) and 13/19 (68.4%) patients, respectively (Table 4).

Table 4. Efficacy Results for TA-TMA Study and Expanded Access Program

	TA-TMA Study	Expanded Access Program (N=19)	
	Adult (N=28)	**Pediatric (n=6)**	**Adult (n=13)**
TMA response 95% CI[a]	17/28 (61%) (40.6, 78.5)	4/6 (67%) (22.3, 95.7)	9/13 (69%) (38.6, 90.9)
Improvement in TMA markers Platelet count LDH	17/28 (61%) 14/23 (61%)[b] 21/28 (75%)	4/6 (67%) 4/6 (67%) 5/6 (83%)	9/13 (69%) 9/13 (69%) 11/13 (85%)
Improvement in organ function	20/27 (74%)[b]	5/6 (83%)	11/13 (85%)
Freedom from red blood cell or platelet transfusion[c]	12/25 (48%)[b]	3/5 (60%)[b]	9/13 (69%)

CI: confidence interval. LDH: lactate dehydrogenase; TA-TMA: transplant-associated thrombotic microangiopathy.

[a] Confidence intervals were calculated using the exact (Clopper-Pearson) method.

[b] These component finding are based on the number of patients with evaluable data.

[c] Defined as no transfusions for at least 4 weeks from the last transfusion; only evaluated patients who received transfusions within the 2 weeks prior to or on the first narsoplimab dose-date.

In the TA-TMA Study, the 100-day survival from time of TMA diagnosis was 73.4% (95% CI: 52.2, 86.4). In the EAP cohort (N = 19), 100-day survival from time of TMA diagnosis was 73.7% (95% CI: 47.9, 88.1).

Practice Guidelines and Position Statements

In response to the lack of consistent diagnostic and prognostic markers for diagnosing transplant-associated thrombotic microangiopathy (TA-TMA), representatives from the American Society for Transplantation and Cellular Therapy, Center for International Bone Marrow Transplant Research, Asia-Pacific Blood and Marrow Transplantation, and European Society for Blood and Marrow Transplantation reviewed literature and developed consensus statements regarding diagnostic and prognostic features of TA-TMA. (2) Consensus key points are noted below:

1. "TA-TMA is independently associated with significant morbidity and mortality. (Category 2A)
2. Harmonization of diagnostic criteria and risk stratification in TA-TMA are critical to better understand the incidence, risk factors, and outcomes of the disease and the impact of TA-TMA-directed therapy. (Category 2A)
3. TA-TMA can be diagnosed via histology (renal or intestinal) or clinically using modified Jodele criteria. (Category 2B)
4. The following features are associated with increased nonrelapse mortality (NRM) in patients with TA-TMA and are considered high-risk features: elevated sC5b-9 (>ULN [upper limit normal]), rUPCR (random urine protein-to-creatinine ratio) (≥1 mg/mg), elevated lactate dehydrogenase (LDH) (≥2 times ULN), grade II-IV acute graft-versus-host disease (GVHD), infections (viral or bacterial), and organ dysfunction. (Category 2A)
5. Specific diagnostic and prognostic biomarkers or biomarker panels are needed for TA-TMA. (Category 2A)

6. Additional studies are needed to determine the impact of TA-TMA directed therapy in patients with high-risk disease, particularly in those with concurrent severe GVHD and infection. (Category 2A)
7. All allogeneic and pediatric autologous hematopoietic cell transplant (HCT) recipients with neuroblastoma should be routinely screened for TA-TMA through day 100. (Category 2B)" (2)

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 (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J1289

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

References

Prescribing Information/Position Statement

1. Prescribing Label: Yartemlea (narsoplimab-wuug) injection, for intravenous use. December 2025. Available at <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm> (accessed on June 2, 2026).
2. Schoettler ML, Carreras E, Cho B, et al. Harmonizing Definitions for Diagnostic Criteria and Prognostic Assessment of Transplantation-Associated Thrombotic Microangiopathy: A Report on Behalf of the European Society for Blood and Marrow Transplantation, American Society for Transplantation and Cellular Therapy, Asia-Pacific Blood and Marrow Transplantation Group, and Center for International Blood and Marrow Transplant Research. Transplant Cell Ther. Mar 2023; 29(3):151-163. PMID 36442770

Other:

3. Lazana I. Transplant-Associated Thrombotic Microangiopathy in the Context of Allogenic Hematopoietic Stem Cell Transplantation: Where We Stand. Int J Mol Sci. Jan 6 2023; 24(2):1159. PMID 36674666
4. Li A and Sartain SE. Transplant-associated TMA: the conundrum of diagnosis and treatment. Hematology Am Soc Hematol Educ Program. Dec 2024; 2024(1):206-213. PMID 39644048

Centers for Medicare and Medicaid Services (CMS)

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 and Medicaid Services (CMS) 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 <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
07/01/2026	New medical document. Narsoplimab-wuug (Yartemlea®) may be considered medically necessary for the treatment of hematopoietic stem cell transplant-associated thrombotic microangiopathy (TA-TMA) when all the following criteria are met: 1. Individual is 2 years of age or older; 2. Individual has hematopoietic stem cell transplant-associated thrombotic microangiopathy diagnosis confirmed by: a. Renal biopsy; OR b. 4 or more of the following: i. Schistocytes; ii. Thrombocytopenia 50% or greater reduction from baseline after engraftment or transfusion dependent; iii. Anemia: 1 g/dL reduction in hemoglobin (Hb) from baseline after engraftment or transfusion dependence; iv. Lactate dehydrogenase (LDH): > upper normal limit; v. Hypertension: >140/90 in individuals 18 years of age or older OR >99th percentile in individuals <18 years of age; vi. Proteinuria: spot urine protein creatinine ratio (uPCR) 1 mg/mg or higher; vii. Elevated sC5b9: greater than the upper normal limit. Narsoplimab-wuug (Yartemlea®) is considered experimental, investigational and/or unproven for all other non-FDA approved indications.