Cablivi (caplacixumab-yhdp) Prior Authorization with Quantity Limit Program Summary

This program applies to FlexRx Closed, FlexRx Open, FocusRx, GenRx Closed, GenRx Open, Health Insurance Marketplace, and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard program.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
06-01-2024	01-01-2020

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Cablivi® (caplacizumab-yhdp) Injection for intravenous or subcutaneous use	Treatment of adult patients with acquired thrombotic thrombocytopenia purpura (aTTP), in combination with plasma exchange and immunosuppressive therapy		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Acquired/immune-mediated thrombotic thrombocytopenic purpura (aTTP/iTTP)	Thrombotic thrombocytopenic purpura (TTP) is a rare medical emergency that is almost always fatal if appropriate treatment is not quickly started. TTP is caused by severely reduced activity of the von Willebrand factor-cleaving protease ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13). Hereditary or congenital TTP (cTTP) accounts for less than 5 percent of cases and is inherited by mutations of the ADAMTS13 gene. More commonly, TTP is acquired and due to ADAMTS13 autoantibodies that inhibit plasma ADAMTS13 activity and is referred to as immune-mediated TTP (iTTP) or acquired TTP (aTTP). More than 95% of all TTP cases are aTTP/iTTP. Patients with TTP present with thrombocytopenia, microangiopathic hemolytic anemia with schistocytes on the blood smear, and various degrees of organ damage.(2,3) Rapid recognition of TTP is crucial to initiate appropriate treatment. The first-line therapy for acute TTP is based on daily therapeutic plasma exchange (PEX) supplying deficient ADAMTS13, with or without steroids. Additional immune modulators targeting ADAMTS13 autoantibodies are mainly based on steroids and the humanized anti-CS20 monoclonal antibody rituximab. In refractory or unresponsive TTP, more intensive therapies including twice-daily PEX; pulses of cyclophosphamide, vincristine, or cyclosporine A; or salvage splenectomy are considered.(3) Complications of TTP may include neurological problems, fever, abnormal kidney function, abdominal pain, and heart problems. An episode of TTP usually occurs suddenly and lasts days or weeks, but may continue for months. Relapses (or

	flareups) can occur in up to 60 percent of people with aTTP/iTTP. The ADAMTS13 enzyme normally helps control the activity of certain blood clotting factors.(4) Distinguishing TTP from other thrombotic microangiopathy (TMA) syndromes is crucial because patients with severe ADAMTS13 deficiency are likely to respond to empirical therapeutic PEX, while those without ADAMTS13 severe deficiency often require treatments other than PEX. To definitely identify TTP out of the other diagnoses is also necessary because it has a specific outcome requiring a well-defined follow-up.(3) Screening for ADAMTS13 activity is the first test to be performed. If ADAMTS 13 activity is less than 10% TTP diagnosis is confirmed. Reference methods for ADAMTS13 activity remain homemade manual methods requiring substantial skill to provide enough reliability for diagnostic use, especially because of preanalytical and analytical limitations. These methods are time-consuming requiring several labor-intensive hours for turnaround results. As a consequence, these reference methods are limited to expert laboratories (usually 1 or 2 laboratories per country worldwide centralizing ADAMTS13 biology and networking with clinical centers involved in the management of patients with TMA). Rapid commercial ELISA assays for ADAMTS13 activity manageable in local laboratories have been developed, but they do not have the accuracy and reliability of the reference methods. These assays are secondary, but in the acute setting, when positive, they reinforce the diagnosis of TTP.(3) Because of these reasons, reliable results of ADAMTS13 investigation usually cannot be available in an emergency. In a large majority of cases, the unavailability of ADAMTS13 data in an emergency is not a limitation to initial management. Urgent therapeutic management is usually decided on the basis of TTP clinical symptoms and not on the basis of ADAMTS13 results. However, ADAMTS13 investigation remains crucial to definitely confirm TTP diagnosis.(3) The International Society on Thrombosis and Haemostasis (ISTH) developed guidelines for diagnosing TTP and prioritizing the initial diagnostic steps involved in confirming TTP during the first acute episode, for the purpose of providing optimal initial treatment to the appropriate patient population. Three diagnostic pathways were identified for a full appraisal:(2) • Scenario A: a pathway where ADAMTS13 activity measurement is readily available (i.e., within 72 hours) • Scenario B: a pathway where ADAMTS13 measurement is NOT available • Scenario C: a pathway where WDAMTS13 activity measurement is available with a delay (i.e., after 72 hours but less than 7 days) The patients with suspected TTP are defined as: patients with thrombocytopenia (platelets less than 100 X 10^9/L), microangiopathic hemolytic anemia (e.g., hemoglobin and hematocrit below the lower limit of the reference range, low haptoglobin, elevated lactase dehydrogenase, the presence of schistocytes in peripheral blood smear), and relatively preserved renal function. The panel discussed the additional value of using a clinical risk assessment model such as the PLASMIC score or the French score but felt it was out of scope for the guidelines at this time.(2) PLASMIC score or French score predictions of likelihood of severe ADAMTS13 deficiency in suspected TTP(2)

Parameters	French Score (points accrued)	PLASMIC Score (points accrued)
Platelet count	Less than 30 X 10^9/L (+1)	Less than 30 X 10^9/L (+1)
Serum creatinine level	Less than 2.26 mg/dL (+1)	Less than 2.0 mg/dL (+1)
Hemolysis • Indirect bilirubin greater than 2 mg/dL • Or reticulocyte count greater than 2.5% Or undetectable haptoglobin	*	(+1)
No active cancer in previous year	*	(+1)
No history of solid organ or stem cell transplant	*	(+1)
INR	*	Less than 1.5 (+1)
MCV	NA	(+1)
Likelihood of severe deficiency of ADAMTS13 activity (i.e., less than 10%)	0:2% 1: 70% 2: 94%	0-4: 0-4% 5: 5%-24% 6-7: 62%-82%

Note: each item is associated with 1 point (+1) as noted
* French score considered patients with thrombotic microangiopathy that included hemolysis and schistocytes in their definition and assumed that there was no history or clinical evidence for associated cancer, transplantation, or disseminated intravascular coagulation. Therefore, these items were intrinsic to the scoring system. NA in MCV: not incorporated in the French score

For patients with iTTP experiencing a first acute event, the ISTH panel gives a strong recommendation for the addition of corticosteroids to PEX over PEX alone. The panel was unable to make a more detailed recommendation on a preferred dosage and type of corticosteroid (e.g., prednisone, methylprednisolone) given the known cardiac, endocrine, and neuropsychiatric adverse effects of corticosteroids on the susceptible patient that will be administered these agents. The panel gave a conditional recommendation for the addition of rituximab to corticosteroids and PEX over corticosteroids and PEX alone.(5)

For patients with iTTP experiencing a relapse, the ISTH panel gives a strong recommendation for the addition of corticosteroids to PEX over PEX alone. The panel made a strong recommendation despite very low certainty evidence because the recommended intervention may moderately reduce the mortality in a life-threatening situation, and its adverse events are not prohibitive over a short term. The panel made a conditional recommendation for the addition of rituximab to corticosteroids and PEX over corticosteroids and PEX alone.(5)

	For patients with iTTP experiencing an acute event (first event or relapse), the ISTH panel gave a conditional recommendation for using caplacizumab over not using caplacizumab. The data informing this recommendation was of moderate certainty, based on two published randomized controlled trials (one of which was double-blinded). Data was not available to differentiate the caplacizumab's effect on the first and relapsed events, so these patients are considered together. The panel noted that the mortality rate was low in both control and caplacizumab arms in both randomized controlled trials. This might not be reflective of the true mortality rates in other TTP studies or patient populations, suggesting the possibility of selection bias meaning the patients in these studies may have had less severe disease. Patients receiving caplacizumab showed a clinically and statistically significant reduction in the number of exacerbations (defined as disease recurrence during therapy or within 30 days after completion of PEX); however, these patients also had a clinically and statistically significant increase in the number of relapses (defined as disease recurrence occurring more than 30 days after completion of PEX therapy) at 12 months. Caplacizumab may leave patients prone to experience a later recurrence owing to the unresolved ADAMTS13 deficiency and inhibitors. The panel also noted that patients on caplacizumab experienced clinically important bleeding side effects.(5)
	
	More specific conditional recommendations were made by the ISTH panel depending on ADAMTS13 testing availability:(2)
	
	• In settings with a timely access to plasma ADAMTS13 activity testing (scenario A or scenario C) and for patients with a high clinical suspicion (greater than or equal to 90% pretest probability) of iTTP (e.g., based on clinical assessment or a formal clinical risk assessment method):
	  • Step 1: Acquire a plasma sample for ADAMTS13 testing before an initiation of PEX or use of any blood product
	  • Step 2: Start PEX and corticosteroids without waiting for the results of ADAMTS13 testing
	  • Step 3: Consider early administration of caplacizumab before receiving plasma ADAMTS13 activity results
	  • Step 4: When the results of plasma ADAMTS13 activity is available, continue caplacizumab if ADAMTS13 activity is less than 10 IU/dL (or 10% of normal) (a positive result) or stop caplacizumab and consider other diagnoses if ADAMTS13 activity is greater than 20 IU/dL (or greater than 20% of normal) (a negative test)
	  • Step 5: For patients with plasma ADAMTS13 activity less than 10 IU/dL (or less than 10% of normal), also consider adding rituximab as early as possible, as a majority of these adult patients (greater than 95%)
	• In settings with a timely access to plasma ADAMTS13 testing (scenario A or scenario C) and for patients with patients with intermediate or low clinical suspicion of iTTP (e.g., based on clinical assessment or a formal clinical risk assessment method):
	  • Step 1: Acquire a plasma sample for ADAMTS13 testing before an initiation of PEX or use of any blood product
	  • Step 2: Consider starting PEX and corticosteroids, depending on the clinician's judgment and assessment of the individual patient
	  • Step 3: Do not start caplacizumab until the result of plasma ADAMTS13 activity becomes available
	  • Step 4: When the results of plasma ADAMTS13 activity testing is available, consider adding caplacizumab and rituximab if ADAMTS13 activity is less than 10 IU/dL (or less than 10% of normal) with inhibitors or an elevated level of anti-ADAMTS13 IgG (a positive result) do not start caplacizumab and consider other diagnoses if

	ADAMTS13 activity is greater than 20IU/dL (or greater than 20% of normal (a negative result) • In settings of no reasonable access to plasma ADMTS13 activity testing (scenario B) do not use caplacizumab regardless of the pretest probability of TTP
Efficacy	The efficacy of Cablivi for the treatment of adult patients with acquired thrombotic thrombocytopenic purpura (aTTP) in combination with plasma exchange (PEX) and immunosuppressive therapy was established in a pivotal multicenter, randomized, double-blind, placebo- controlled trial (HERCULES) (NCT02553317). 72 patients were randomized to receive Cablivi and 73 patients received placebo. Patients in both groups received PEX and immunosuppressive therapy. The efficacy of Cablivi in patients with aTTP was established based on time to platelet count response (platelet count greater than or equal to 150,000/µL followed by cessation of daily PEX within 5 days). Time to platelet count response was shorter among patients treated with Cablivi compared to placebo. Treatment with Cablivi resulted in a lower number of patients with TTP-related death, recurrence of TTP, or at least one treatment-emergent major thromboembolic event (a composite endpoint) during the treatment period. Recurrence of TTP was defined as a new decrease in platelet count after initial normalization, requiring PEX therapy to be reinitiated. A recurrence within 30 days after completion of PEX therapy was defined as an 'exacerbation'. A recurrence occurring more than 30 days after completion of PEX therapy was defined as a 'relapse'.(1) During the treatment period and 28-day follow-up, treatment with caplacizumab was associated with a significantly shorter time to platelet normalization, compared with placebo: 2.69 days (95% CI 1.89-2.83] versus 2.88 days (95% CI 2.68-3.56; p=0.01). The authors also reported that caplacizumab-treated patients were 1.55 times more likely than placebo-treated patients to have a normalization of the platelet count at any time point (p= 0.01).(6) Caplacizumab significantly outperformed standard-of-care alone in other secondary outcomes, including:(3) • composite of TTP-related death, TTP recurrence, or a thromboembolic event: 12% vs. 49% (p less than 0.001) • recurrence of TTP at any time: 12% vs. 38% (p less than 0.001) Disease exacerbation occurred in 31 patients (28 in the placebo group and 3 in the caplacizumab group). Of these, 28 had an unresolved autoimmune disease that may have been the underlying culprit, the researchers noted.(6) Health-care resource use also appeared lower in the caplacizumab group: In the placebo group, patients required an average of 9.4 days of plasma-exchange therapy, compared with 5.8 days in the caplacizumab group. This represented a 38-percent shorter duration of treatment and a 41-percent lower volume of PEX (p values not reported). Duration of hospitalization and intensive care unit stays were reduced, as well.(6)
Safety	Cablivi is contraindicated in patients with a previous severe hypersensitivity reaction to caplacizumab-yhdp or any of its excipients. (1) Cablivi should be discontinued if the patient experiences more than 2 recurrences of aTTP, while on Cablivi.(1)

REFERENCES

Number	Reference
1	Cablivi prescribing information. Genzyme Corporation. April 2023.
2	Zheng, X. L., Vesely, S. K., Cataland, S. R., Coppo, P., Geldziler, B., Iorio, A., Matsumoto, M., Mustafa, R. A., Pai, M., Rock, G., Russell, L., Tarawneh, R., Valdes, J., & Peyvandi, F. (2020). ISTH guidelines for the diagnosis of thrombotic thrombocytopenic purpura. *Journal of Thrombosis and Haemostasis*, *18*(10), 2486–2495. https://doi.org/10.1111/jth.15006
3	Joly, B. S., Coppo, P., & Veyradier, A. (2017). Thrombotic thrombocytopenic purpura. *Blood*, *129*(21), 2836–2846. https://doi.org/10.1182/blood-2016-10-709857
4	U.S. Department of Health & Human Services. *Thrombotic thrombocytopenic purpura, acquired*. Genetic and Rare Diseases Information Center. https://rarediseases.info.nih.gov/diseases/4607/thrombotic-thrombocytopenic-purpura-acquired/
5	Zheng, X. L., Vesely, S. K., Cataland, S. R., Coppo, P., Geldziler, B., Iorio, A., Matsumoto, M., Mustafa, R. A., Pai, M., Rock, G., Russell, L., Tarawneh, R., Valdes, J., & Peyvandi, F. (2020). ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. *Journal of Thrombosis and Haemostasis*, *18*(10), 2496–2502. https://doi.org/10.1111/jth.15010
6	ASH Publications. (2019, March). Ashpublications.org. Clinical News. Bleeding disorders. https://ashpublications.org/ashclinicalnews/news/4356/Caplacizumab-Improves-Platelet-Normalization-Time

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Cablivi	caplacizumab-yhdp for inj kit	11 MG	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Cablivi	Caplacizumab-yhdp for Inj Kit 11 MG	11 MG	58	Vials	365	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Cablivi	caplacizumab-yhdp for inj kit	11 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Cablivi	Caplacizumab-yhdp for Inj Kit 11 MG	11 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of acquired thrombotic thrombocytopenia purpura (aTTP) **AND** 2. The diagnosis has been confirmed by ONE of the following (medical records required): A. BOTH of the following: 1. The patient has severe thrombocytopenia (i.e., a platelet count less than 100 X 10^9/L) **AND** 2. The patient has microangiopathic hemolytic anemia (e.g., hemoglobin and hematocrit below the lower limit of the reference range, low haptoglobin, elevated lactase dehydrogenase, the presence of schistocytes in peripheral blood smear) **OR** B. The patient has a positive ADAMTS13 activity result (i.e., less than 10 IU/dL [or less than 10% of normal]) **AND** 3. If the patient has an FDA labeled indication, ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 4. ONE of the following: A. The patient will be using immunosuppressive therapy (e.g., corticosteroids, rituximab, cyclophosphamide, mycophenolate mofetil) in combination with the requested agent **OR** B. The patient has an intolerance, hypersensitivity, or FDA labeled contraindication to immunosuppressive therapy **AND** 5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval**: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. BOTH of the following A. The patient had at least one occurrence of acquired thrombotic thrombocytopenic purpura (aTTP) during the current course of therapy **AND** B. The patient has NOT had more than 2 occurrences of aTTP while using the requested agent during the current course of therapy **OR** 3. The patient had a relapse/recurrence of aTTP after completion of a course of therapy and requires an additional course of therapy **Length of Approval:** Occurrence of aTTP on current course of therapy - requested number of vials up to 58 vials/365

Module	Clinical Criteria for Approval
	days; Relapse of aTTP - 58 vials/365 days