



## CADTH Reimbursement Recommendation

# Caplacizumab (Cablivi)

**Indication:** For the treatment of adults with acquired thrombotic thrombocytopenic purpura in combination with plasma exchange and immunosuppressive therapy

**Sponsor:** Sanofi-Aventis Canada Inc.

**Final recommendation:** Do not reimburse



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# Summary

## What Is the CADTH Reimbursement Recommendation for Cablivi?

CADTH recommends that Cablivi should not be reimbursed by public drug plans for the treatment of adults with acquired thrombotic thrombocytopenic purpura (aTTP) in combination with plasma exchange (PE) and immunosuppressive therapy.

### Why Did CADTH Make This Recommendation?

- Evidence from clinical trials were unable to demonstrate that Cablivi improved survival and quality of life, minimized organ damage, or prevented long-term aTTP recurrence. Although results showed that Cablivi reduced time to platelet normalization compared with placebo in patients with aTTP who received PE and immunosuppressive therapy, CADTH Canadian Drug Expert Committee was unable to determine how this correlated with the previously mentioned clinical outcomes.
- Evidence from an integrated analysis of clinical trials and several sources of real-world evidence were unable to clearly demonstrate whether Cablivi provides benefits when added to PE and immunosuppressive therapy due to limitations associated with the methodology.
- Based on the evidence reviewed, it remains uncertain whether Cablivi meets the needs identified by patients of improving survival and quality of life, preventing disease complications, reducing the need for PE, and preventing disease recurrence.

### Additional Information

#### What Is Acquired Thrombotic Thrombocytopenic Purpura?

aTTP is a rare blood disorder in which blood clots form in small blood vessels, resulting in low platelet counts. In Canada, approximately █ patients were treated for TTP in 2018.

#### Unmet Needs in Acquired Thrombotic Thrombocytopenic Purpura

Some patients do not respond to currently available treatments (PE plus immunosuppression using corticosteroids with or without rituximab) and experience persistent formation of clots in small blood vessels leading to complications such as stroke, myocardial infarction, changes in mental status, kidney damage, and death. Other patients respond to initial treatment but subsequently experience disease recurrence. In both groups of patients, there is an unmet need for additional treatment options that



# Summary

improve survival and prevent the short- and long-term consequences of abnormal clot formation.

## **How Much Does Cablivi Cost?**

Treatment with Cablivi is expected to cost approximately \$223,200 per patient per aTTP episode in addition to the cost of standard of care.

## Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that caplacizumab not be reimbursed for the treatment of adults with acquired thrombotic thrombocytopenic purpura (aTTP) in combination with plasma exchange (PE) and immunosuppressive therapy (IST).

## Rationale for the Recommendation

As outlined in the 2020 CDEC final recommendation for caplacizumab, 1 phase III, double-blind, randomized controlled trial (RCT) (HERCULES; N = 145) in adults with aTTP receiving PE and IST demonstrated that treatment with caplacizumab statistically significantly reduced the time to normalization of platelet count. However, this study was not designed to assess the effects of caplacizumab on the clinically important outcomes of survival, reduction in organ damage, health care use, or long-term recurrence of aTTP. Given caplacizumab's mechanism of action, CDEC could not determine the clinical magnitude of the correlation between time to normalization of platelet count with the aforementioned clinical outcomes. In addition, the median time to platelet normalization was 2.69 days in the caplacizumab treatment group and 2.88 days in the placebo group, and the difference between treatment groups was of unknown clinical relevance. As part of the evidence base for the resubmission, CDEC considered other studies including a long-term follow-up study (post-HERCULES; N = 104), a post hoc integrated analysis of data from the HERCULES and TITAN trials (N = 220), and several real-world evidence (RWE) studies. Several methodological limitations in the reviewed studies precluded CDEC from determining whether caplacizumab provides clinically meaningful value compared with PE plus IST alone. Further, no definitive conclusion could be reached regarding the effects of caplacizumab on health-related quality of life (HRQoL) from the post-HERCULES trial given the exploratory nature of the analyses, the open-label design, variable rates of missing data, and uncertainty in the measurement properties of the patient-reported outcomes instruments in patients with aTTP.

Patients described their aTTP as having a significant impact on their quality of life and identified a need for effective treatments that improve survival and quality of life, prevent disease complications, reduce recurrence rates, reduce the need for PE, and have fewer side effects. While recognizing the need for additional effective treatment options for this patient population, there was uncertainty whether caplacizumab met these important therapeutic needs given the limitations associated with the evidence reviewed.

## Discussion Points

- The sponsor requested a reconsideration of the initial draft recommendation to not reimburse caplacizumab for the treatment of adults with aTTP in combination with PE and IST. CDEC discussed each of the issues identified by the sponsor in their Request for Reconsideration.
- During the initial and reconsideration meetings, CDEC noted that although aTTP is a rare and serious condition, the nature of the disease and administration of current therapies does permit for well-

designed randomized trials to be conducted. During the reconsideration meeting, CDEC discussed that although there are challenges in recruiting patients and evaluating clinically meaningful outcomes for aTTP, it may be feasible to conduct a well-designed randomized trial in jurisdictions where caplacizumab is not part of the standard of care (SOC).

- During the initial and reconsideration meetings, CDEC considered that there is currently an unmet need for treatment options that improve patients' survival while preventing aTTP complications and their sequelae and associated disabilities. CDEC acknowledged input from the clinical experts that this unmet need is primarily in patients who have refractory or recurrent aTTP and in patients who are critically ill with end-organ dysfunction. Based on available evidence, CDEC concluded that currently there is insufficient evidence to inform a recommendation on a subset of patients most likely to respond to caplacizumab in combination with PE and IST.
- An outcome identified as important to patients is a reduction in the risk and rate of experiencing relapses of aTTP. The design and duration of the HERCULES study were insufficient to assess the effects of caplacizumab on the rate of relapse (i.e., recurrent thrombocytopenia occurring after the 30-day post-daily PE period) beyond the trial's duration. The post-HERCULES study (a 3-year follow-up study of patients who completed the HERCULES study) evaluated long-term aTTP relapse in patients who did not experience an aTTP recurrence during the HERCULES study or before the beginning of the post-HERCULES study (i.e., efficacy intention-to-observe [ITO] population). The data from the post-HERCULES study did not provide a signal that caplacizumab resulted in more frequent aTTP relapses after PE discontinuation compared with placebo. During the initial and reconsideration meetings, CDEC was unable to conclude that caplacizumab reduced aTTP recurrence rates because the post-HERCULES trial enrolled an enriched population, excluded patients who experienced more than 2 episodes of aTTP, lacked formal statistical testing, and had high rates of missing data at later time points in the follow-up period. These limitations contribute substantial uncertainty to the study results. The clinical expert consulted by CADTH indicated that relapse and recurrence rates are a function of immunosuppression, which is not in keeping with the mechanism of action of caplacizumab which prevents platelet aggregation and development of microthrombi.
- A post hoc integrated analysis of HERCULES and TITAN data evaluated survival, health care use, organ damage, and refractory aTTP. The committee noted that results appeared overall consistent with those of the 2 individual studies. However, given it was unclear if the data pooling was appropriate and the lack of inferential statistical testing among other limitations, CDEC concluded that the data were insufficient to draw conclusions. During the reconsideration meetings, CDEC noted that it was not clear that the integrated analysis, including pooled efficacy analysis across the HERCULES and TITAN studies, was prospectively planned with prespecified hypotheses to be tested statistically. Therefore, there is an increased risk of detecting false-positive associations and the results of the pooled analysis were considered hypothesis generating and interpreted in exploratory fashion.

- RWE studies (comparing patients treated with caplacizumab with historical controls who received SOC) provided supportive evidence on survival, health care use, and refractory aTTP. However, due to the potential for biased patient selection and intergroup differences in measured and/or unmeasured confounding variables, no firm conclusions could be drawn on the results of these studies. The evidence reviewed as part of the reimbursement review in 2020, the resubmission, and this reconsideration were associated with substantial uncertainty, as noted in the Rationale for the Recommendation section. In addition to uncertainty associated with the magnitude of the treatment effect, CDEC remained unable to identify patients who may benefit most from treatment with caplacizumab. In addition, during the reconsideration meeting, CDEC noted that new treatments that decrease the risks of mortality, acute events (e.g., acute myocardial infarction, stroke, cognitive impairment), and chronic events (e.g., major thrombotic events, renal insufficiency, arterial hypertension) in all patients with aTTP are needed. However, there is no direct evidence that conclusively demonstrates that caplacizumab reduces mortality, decreases the acute consequences of microvascular thrombosis or chronic major thrombotic events or prevents organ damage.
- According to clinical experts consulted by CADTH, the percentage of patients who received rituximab in the HERCULES study and the RWE cohort studies was higher than would be expected in Canada. Given that 40% of patients in the overall HERCULES trial period received caplacizumab in addition to rituximab (and PE plus corticosteroids), it is unclear if the observed effects of caplacizumab in the trial would be observed in Canadian practice. The committee agreed that currently there is insufficient evidence to determine the effect of concomitant use of rituximab on the overall study outcomes. During the reconsideration meetings, CDEC noted that the lack of control for baseline rituximab use in the RWE does limit the interpretation of the treatment effect with caplacizumab.
- During the initial meeting and reconsideration meetings, CDEC discussed that the HERCULES trial suggested that treatment with caplacizumab may reduce the total PE volume and decrease duration of PE therapy compared with placebo. Patient input received indicated that there is a need for effective treatments that reduce the total volume and decrease duration of PE therapy. However, given that no prespecified statistical comparisons were conducted in the analysis of these data, that imbalances existed in the baseline characteristics of the 2 groups, and there was a lack of long-term clinical outcome data, CDEC was unable to interpret these findings. The committee discussed that results from the integrated analyses and the RWE studies were supportive of a reduced need for PE. However, given the aforementioned limitations with both data sources, CDEC concluded that the data were insufficient to draw firm conclusions. This was again considered by CDEC during the reconsideration discussion. CDEC acknowledged that reducing PE volume and duration of hospitalization were outcomes important to patients but maintained that, based on the evidence reviewed from the HERCULES, post-HERCULES, and TITAN studies and the 2 comparative RWE studies, no robust conclusions could be drawn regarding these outcomes (refer to the Clinical Evidence section for a detailed summary of the limitations associated with each of these studies).
- During the reconsideration meeting, CDEC discussed that jurisdictions should insure equitable access across treatment centres to current SOC for the treatment of adult patients with aTTP.

## Background

TTP is an ultra-rare blood disorder caused by reduced enzymatic activity of the von Willebrand factor–cleaving protease a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS13), resulting in an inability to cleave high-molecular-weight von Willebrand factor multimers and, as a consequence, and the formation of platelet-rich blood clots in small vessels (thrombotic microangiopathy). TTP is a medical emergency and aTTP (driven by autoantibodies against ADAMTS13) is the dominant form. Mortality is estimated at approximately 10% to 20%; in addition, thrombotic complications and their sequelae contribute to persistent cognitive and physical difficulties that can be life-altering in some patients, compromising HRQoL. After the presenting episode, recurrence of aTTP (exacerbation: recurrence within 30 days of cessation of PE; relapse: recurrence after 30 days of cessation of PE) will occur in up to half of patients, while refractory aTTP (no platelet count increase following treatment) will occur in approximately 10% of patients. The incidence of aTTP is estimated at approximately 2 to 4 cases per million people per year (approximately 5.5 cases per million adults); approximately █ patients with TTP were treated in Canada in 2018. According to the clinical experts consulted by CADTH, current management of aTTP in Canada involves PE and immunosuppression with corticosteroids. In Canada, rituximab is typically not used upfront and is administered to patients with aTTP exacerbations, relapsed aTTP, or refractory aTTP. The main goals of treatment are to prolong life and avoid mortality while preventing thrombotic complications and associated disabilities.

Caplacizumab has been approved by Health Canada for the treatment of adults with aTTP in combination with PE and IST. Caplacizumab is a bivalent humanized nanobody and an antithrombotic drug and platelet aggregation inhibitor. It is available as a powder for solution (11 mg); the dosage recommended in the product monograph is 11 mg IV and 11 mg subcutaneous [SC] injections on day 1 of PE followed by daily 11 mg SC injections during PE and for a minimum of 30 days after cessation of PE.

## Submission History

Caplacizumab was initially reviewed by CADTH for the treatment of adults with aTTP in combination with PE and IST and received a negative funding recommendation from CDEC on September 1, 2020. The original CADTH review of caplacizumab included 1 phase III, double-blind RCT (HERCULES, N = 145) and supportive evidence from 1 phase II, multicentre, single-blind, parallel design, placebo-controlled RCT (TITAN, N = 75) that evaluated the efficacy and safety of caplacizumab in adult patients with aTTP. Key reasons for the recommendation included insufficient evidence of clinically important outcomes (e.g., survival, organ damage, health care use, or long-term aTTP recurrence), lack of long-term clinical outcome data, lack of an identifiable subpopulation most likely to benefit from treatment, generalizability to Canadian clinical practice, and absence of HRQoL data.

The drug was resubmitted for review by the sponsor on the basis of the availability of new data to address the evidence gaps identified by CDEC with the 2020 review. The sponsor submitted a prospective long-term follow-up study of patients who completed the HERCULES study (post-HERCULES); a variety of post hoc

analyses, including an integrated analysis of data from HERCULES and TITAN studies; and several RWE studies, including comparisons of patients treated with caplacizumab with historical controls who received SOC alone in France and the UK.

## Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III RCT trial (HERCULES) in adult patients with aTTP and its prospective, long-term follow-up study (post-HERCULES) in patients who completed the HERCULES trial; supportive data from 1 phase II RCT (TITAN) in patients with aTTP; supportive data from a post hoc integrated analysis of the HERCULES and TITAN trials; and supportive data from 2 RWE cohorts from France and the UK
- patients' perspectives gathered by 1 patient group, the Answering TTP Foundation
- input from public drug plans and cancer agencies that participate in the CADTH review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with aTTP
- input from 1 clinician group, the Canadian Apheresis Group
- a review of the pharmacoeconomic model and report submitted by the sponsor
- information submitted as part of the Request for Reconsideration (described subsequently).

## Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from clinical experts consulted by CADTH for the purpose of this review.

### Patient Input

One patient group, the Answering TTP Foundation, provided input for this review. The group conducted an online survey in May and June 2022 (N = 49 respondents, including 31 patients with aTTP; 16 family members, caregivers, or friends of patients with aTTP; 1 health care professional; and 1 researcher). Most survey respondents were women (80%), and most were living in Canada (90%). Approximately half of respondents (48%) had experienced at least 1 relapse. Patients highlighted delays in diagnosis and treatment as well as the negative effects of serious and/or frequent symptoms of aTTP (e.g., bruising, fever, fatigue, migraine, confusion, abdominal pain, bleeding, shortness of breath, vision loss, and jaundice), which impose heavy burdens on mental health (e.g., anxiety, depression, and panic attacks). A subset of patients experienced incapacitating or life-threatening complications of aTTP, including stroke, myocardial infarction, and kidney problems. Nearly all patients had experience with PE and corticosteroids, and approximately two-thirds (65%) had experience with rituximab. Respondents described the challenges of current treatments, including lengthy hospital stays, side effects of corticosteroids, and the inconvenience of daily PE; in addition, available treatments are costly, require time off from work, and may require travel to a major

centre for access. Respondents identified an unmet need for treatments that can reduce the risk of death or disability from aTTP and ease the mental and emotional burdens of disease (e.g., continuous fear of relapse, risk of treatment failure, and effects on social life and career goals). Specifically, respondents valued new treatments that enable patients to survive an aTTP crisis and reduce the likelihood of disease recurrence, thereby reducing the patient's emotional uncertainty in the early stages of an aTTP episode and improving peace of mind during remission. As well, respondents noted that a reduction in the number of PE treatments and ability to plan for the future were important when considering treatment options. Approximately one-third (34%) of respondents had experience with caplacizumab and felt that the drug had contributed to shorter hospitalization, faster remission, and prevention of further disease.

## Clinician Input

### Input From Clinical Experts Consulted by CADTH

Two clinical specialists with expertise in the diagnosis and management of aTTP provided input for this review. The clinical experts stated that although currently available treatments (PE plus immunosuppression with corticosteroids with or without rituximab) are effective in many patients, not all patients manifest durable responses and thus experience persistent or recurrent thrombotic microangiopathy, which can lead to thrombotic complications and, potentially, mortality. According to the clinical experts, there is an unmet need for additional treatment options, especially for patients with aTTP recurrence or refractory aTTP. The clinical experts relayed that caplacizumab would be administered in combination with PE and IST. The clinical experts felt that because some patients respond well to PE and IST, caplacizumab may be a reasonable option to be reserved for patients with aTTP recurrence or refractory aTTP because these patients currently have limited treatment options. The clinical experts acknowledged that it is currently unclear if delaying access to caplacizumab may affect its efficacy. The HERCULES trial was designed to evaluate the upfront use of caplacizumab in combination with PE and IST. The clinical experts also felt that upfront treatment with caplacizumab would be considered in high-risk patients who have neurologic or cardiac abnormalities (including elevated troponin) or are otherwise critically ill. The clinical experts acknowledged that currently there is insufficient evidence to identify patients who are more likely to respond to caplacizumab in combination with PE plus immunosuppression. The clinical experts stated that clinically meaningful responses to caplacizumab plus PE and immunosuppression would be defined by normalization of platelet count (complete blood count) and lactate dehydrogenase (LDH) level. Reticulocyte count, unconjugated bilirubin, hemoglobin, haptoglobin, creatinine, ADAMTS13 activity, and ADAMTS13 autoantibody levels should also normalize. The clinical experts relayed that although the ultimate mechanistic goal of therapy is to normalize ADAMTS13 activity, results of ADAMTS13 testing are generally not readily available in a timely manner as compared with platelet count. According to the clinical experts, PE is typically discontinued after 5 days if platelet count, LDH, and other markers are normalized. Patients are then typically monitored for 1 to 2 days while in hospital to see if their platelet counts drop again or if the hemolytic markers show signs of aTTP recurrence. If there is no evidence of aTTP recurrence, patients are typically discharged from hospital with a corticosteroid taper plan and close outpatient follow-up. The clinical experts stated that patients receiving caplacizumab who develop aTTP recurrence or refractory aTTP would be discontinued from therapy, as would patients with serious toxicities such as clinically significant

bleeding. The clinical experts relayed that 1 of the challenges of using caplacizumab is that it directly increases platelets through its mechanism, potentially masking an indicator of aTTP disease activity, which would make it difficult to determine when it is time to taper PE.

### **Clinician Group Input**

Clinician group input was received from the Canadian Apheresis Group, with 5 clinicians contributing to the submission. No major contrary views from those provided by the clinical experts consulted by CADTH for this review were presented. The clinician group echoed the inability of current treatments to accomplish the goals of therapy (avoid mortality and prevent thrombotic complications) in all patients and the unmet need for additional treatment options for patients with aTTP exacerbations, relapsed aTTP, and refractory aTTP as well as patients at high risk of mortality and/or organ damage. The clinician group also highlighted the unmet need for drugs that can rapidly inhibit platelet aggregation while waiting for PE and immunosuppression to take effect.

### **Drug Program Input**

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially affect the implementation of a CADTH recommendation for caplacizumab:

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

## **Clinical Evidence**

### **Pivotal Studies and Protocol-Selected Studies**

#### **Description of Studies**

The phase III HERCULES trial and phase II TITAN trial were reviewed in the original 2020 CADTH Clinical Review Report for the original caplacizumab submission and were considered relevant evidence for this review. The primary outcome in both studies was time to platelet response. Statistically tested secondary outcomes in the HERCULES study included the composite end point of aTTP-related events (aTTP-related death, recurrence of aTTP, or at least 1 major thromboembolic event), proportion of patients with aTTP

recurrence, proportion of patients with refractory aTTP, and time to normalization of all 3 organ damage markers: LDH, cardiac troponin, and serum creatinine. There were no statistically tested secondary outcomes in the TITAN study. Both studies documented statistically significant differences in time to platelet count response; these were viewed by the clinical experts consulted by CADTH for the 2020 review as too small to be clinically relevant. In the HERCULES study, the proportion of patients randomized to receive caplacizumab who experienced recurrence during the HERCULES overall study period was statistically significantly lower compared with patients randomized to receive SOC. Differences between study randomization arms in the proportion of patients with refractory aTTP were not statistically significant, precluding further statistical testing. The duration and volume of daily PE was shorter in the caplacizumab arm, which the clinical experts consulted by CADTH felt was encouraging and potentially clinically relevant. In addition, the durations of hospitalization and intensive care unit stays were shorter for patients in the caplacizumab arm, but missing data and absence of statistical testing prevented interpretation of these results. Analysis of mortality and time to normalization of organ damage markers numerically favoured caplacizumab but without formal, prespecified statistical testing, these differences could not be interpreted.

One phase III, prospective, long-term, follow-up study of adult patients with aTTP who completed the HERCULES study (post-HERCULES, N = 104) contributed new evidence to this resubmission. The objectives of the post-HERCULES study were to evaluate long-term safety and efficacy of caplacizumab, to evaluate the safety and efficacy of repeated use of caplacizumab in participants who experienced a recurrence of aTTP, and to characterize the long-term clinical impact of aTTP. Following the final 4-week follow-up visit in HERCULES, adult patients with aTTP were invited to enrol in the post-HERCULES study within 1 month. Patients who were not able or willing to comply with study protocol procedures or who enrolled in a clinical study with another investigational drug or device were excluded. Following enrolment at 43 centres in Europe, the US, Canada (3 centres), and Israel, patients were followed for a period of 3 years. Patients attended twice-yearly visits, starting with a baseline visit coinciding with or occurring within 1 month of the final 28-day follow-up visit in the HERCULES study. During the 3-year follow-up period, patients could receive open-label (OL) caplacizumab in combination with PE and immunosuppression (administered as in the HERCULES study, except that 1 PE could be given before initiation of caplacizumab) for aTTP recurrence (defined as recurrence of thrombocytopenia requiring initiation of daily PE).

The overall ITO population (N = 104) was used for analysis of safety. The efficacy ITO population (N = 78; patients within the overall ITO population who had not experienced aTTP recurrence in the HERCULES study or before the beginning of post-HERCULES) was used for analysis of efficacy based on twice-yearly follow-up visits. The recurrence population (N = 19; patients in the overall ITO population who experienced at least 1 aTTP recurrence during the post-HERCULES study) was used for analysis of data collected during recurrence periods.

All patients who completed the HERCULES study (n = 108) were eligible for the post-HERCULES study, and 104 (96.3%) participated. Approximately two-thirds of participants in the post-HERCULES study were women (71.2%), approximately two-thirds (70.2%) were white, and the average age was 47.5 years. Note that patients were disease-free at the post-HERCULES baseline and thus the average ADAMTS13 activity was 62.1%.

## Efficacy Results

In the efficacy ITO population, consisting of patients who completed HERCULES, enrolled in the post-HERCULES study, and had not experienced an aTTP recurrence in either the HERCULES study or before the beginning of the post-HERCULES study, aTTP-related events (aTTP-related death, recurrence of aTTP, or major thromboembolic events) occurred in 4 patients (8.2%) randomized to receive caplacizumab in HERCULES and in 11 patients (37.9%) randomized to receive SOC alone in the HERCULES study. No patients randomized to receive caplacizumab in the HERCULES study and 1 patient (3.4%) randomized to receive SOC in the HERCULES study died during the post-HERCULES study. Four patients (8.2%) randomized to receive caplacizumab in the HERCULES study and 8 patients (27.6%) randomized to receive SOC in the HERCULES study experienced recurrence of aTTP during the post-HERCULES study. Four patients (8.2%) randomized to receive caplacizumab in the HERCULES study and 11 patients (37.9%) randomized to receive SOC in the HERCULES study experienced major thromboembolic events during the post-HERCULES study; major thromboembolic events other than aTTP occurred in no patients randomized to receive caplacizumab in the HERCULES study and in 3 patients (10.2%) randomized to receive SOC in the HERCULES study.

## Harms Results

In the overall ITO population, 68 patients (90.7%) treated with caplacizumab in the HERCULES study and 26 patients (89.7%) treated with SOC only in the HERCULES study experienced adverse events during the post-HERCULES study. Twenty-eight patients (37.3%) treated with caplacizumab in the HERCULES study and 16 patients (55.2%) treated with SOC only in the HERCULES study experienced serious adverse events during the post-HERCULES study. No patients treated with caplacizumab and 1 patient (3.4%) treated with SOC only in the HERCULES study died during the post-HERCULES study. Sixteen patients (21.3%) treated with caplacizumab in the HERCULES study and 9 patients (31.0%) treated with SOC only in the HERCULES study experienced at least 1 bleeding event during post-HERCULES (based on Standardized Medical Dictionary for Regulatory Affairs query "haemorrhage" excluding the preferred term "aTTP").

## Critical Appraisal

Many of the internal validity issues of the HERCULES study affect the post-HERCULES study as well. Only patients who completed the HERCULES study (108 of 145; 74.5%) were eligible for the post-HERCULES study, and that study provides no information about patients who discontinued the HERCULES study. Higher proportions of caplacizumab-naive patients ( $n = 6$ ; 20.7%) than patients who received caplacizumab in the HERCULES study ( $n = 5$ ; 6.7%) discontinued the post-HERCULES study. The clinical experts consulted by CADTH for this review did not expect that any resulting biases would be directional in favour of caplacizumab. Due to variable rates of missing data, lack of formal statistical testing, potential for bias in patient-reported outcomes in an OL study, and uncertainty in the measurement properties of these instruments in patients for aTTP, changes in HRQoL over time and between the arms of the post-HERCULES efficacy ITO population could not be interpreted.

Many of the external validity issues of the HERCULES study affect the post-HERCULES study as well. The clinical experts consulted by CADTH felt that the post-HERCULES study population was generally reflective of adult patients with aTTP in Canada. Mortality rates in the HERCULES and post-HERCULES studies were lower

than expected in routine clinical practice and patients may have been observed and followed by health care teams for aTTP recurrence and/or thromboembolic events more vigilantly compared with real-world practice. The clinical experts consulted by CADTH stated that the duration of follow-up in the post-HERCULES study was adequate to assess both early recurrence of aTTP (within the first month of presentation) and later recurrences (which often occur within the 2 years following cessation of PE). In the post-HERCULES study, caplacizumab could be administered following up to 1 administration of PE, but this was not a requirement as it was in the HERCULES study. Approximately half (6 of 13; 46.2%) of patients treated with caplacizumab for their first recurrence in the post-HERCULES study also received rituximab. The clinical experts consulted by CADTH for this review noted that the proportion of patients in Canada with aTTP who receive upfront rituximab in addition to PE and corticosteroids is not known with certainty but is likely lower than in the post-HERCULES trial. However, the proportion in clinical practice has increased in recent years due to improved access to rituximab.

### Indirect Comparisons

No indirect evidence was identified for this review.

### Other Relevant Evidence

Six post hoc analyses were included in the sponsor's resubmission: a publication of an integrated analysis of the HERCULES study and the TITAN study as well as 4 posters and 1 abstract describing subgroup analyses of data from the HERCULES and post-HERCULES studies by rituximab use in the HERCULES study, subgroup analyses of data from the HERCULES study by baseline disease severity and time to platelet count response, and a subgroup analysis of patients in the HERCULES study who had suboptimal responses to PE. Because of their post hoc design and incomplete description, the results of the posters and abstracts were excluded from the main body of the CADTH Clinical Report and described in the appendices for reference only.

In addition, an RWE study of a German cohort of patients included in the sponsor's submission was not considered by the CADTH Review Team to address an important gap in the evidence due to the lack of a comparison between patients who received caplacizumab and patients who did not receive caplacizumab. Four abstracts describing other RWE cohorts were not described in sufficient detail to enable the CADTH Review Team to rigorously evaluate their conduct and reporting.

### Post Hoc Analyses

#### *Description of Studies*

Peyvandi et al. (2021) conducted an integrated analysis of data from the HERCULES and TITAN trials as suggested by the US FDA to increase statistical power for assessing treatment differences in efficacy and safety outcomes between caplacizumab and placebo. The integrated analysis included all randomly assigned patients from the HERCULES and TITAN studies, which were described in detail in the Clinical Review report for the Reimbursement Review of caplacizumab in 2020. This study provided an additional evaluation of the clinically important outcomes of mortality, organ damage, health care utilization, and refractory aTTP, but did not address long-term aTTP recurrence.

For the primary analysis of time to platelet count response, treatment groups were compared using a 2-sided log-rank test stratified by trial based on a Kaplan-Meier analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using a Cox proportional hazards model with time to platelet count response as a dependent variable, treatment group as an independent variable, and study as a random effect. To compare secondary outcomes (time to normalization of organ damage markers, duration of PE, proportion of patients with aTTP-related death, aTTP recurrence, or major thromboembolic events, and aTTP recurrence) between treatment groups, a stratified Cochran-Mantel-Haenszel test was used as a stratification factor in the trials. Analysis of time to first normalization of organ damage markers was performed for the primary analysis of time to platelet count response.

### ***Efficacy Results***

During blinded study drug treatment, no patients randomized to receive caplacizumab and 4 patients (3.6%) randomized to receive placebo died; during the overall study periods, 1 patient (0.9%) who was randomized to receive caplacizumab and 5 patients (4.5%) who were randomized to receive placebo died. The proportion of patients who experienced aTTP-related events (aTTP-related death, major thromboembolic events, or aTTP exacerbation) while receiving the blinded study drug treatment was 13.0% (14 of 108) of patients who were randomized to receive caplacizumab versus 47.3% (53 of 112) of patients randomized to receive placebo. During the blinded study drug treatment, no patients who were randomized to receive caplacizumab and 8 patients (7.1%) who were randomized to receive placebo had refractory aTTP. Consistent with the individual studies, treatment with caplacizumab resulted in a numerically faster time to normalization of LDH (HR = 1.43; 95% CI, 1.04 to 1.96), numerically faster time to normalization of troponin (HR = 1.32; 95% CI, 0.86 to 2.04), and numerically faster time to normalization of serum creatinine (HR = 1.68; 95% CI, 0.89 to 3.15). During the overall treatment periods, the median duration of PE was numerically shorter for patients randomized to receive caplacizumab (median = 5.0 days; range, 1 to 35 days) compared with patients randomized to receive placebo (median = 7.5 days; range, 2 to 46 days). During the treatment-free follow-up periods, 14 patients (13.0%) randomized to receive caplacizumab and no patients randomized to receive placebo experienced an aTTP relapse.

### ***Harms Results***

The safety data for the integrated safety population were consistent with the results of the individual studies and no new safety signals were identified. Bleeding excluding aTTP occurred in 58.5% of patients treated with caplacizumab and 42.7% of patients treated with placebo. Serious bleeding excluding aTTP occurred in 11.3% of patients treated with caplacizumab and 1.8% of patients treated with placebo.

### ***Critical Appraisal***

Overall, the results of the integrated analysis supported and reinforced the consistent numeric improvements in the clinically important outcomes of survival, refractory aTTP, and duration of PE observed in the clinical development program (phase II TITAN and phase III HERCULES studies). However, internal and external validity issues of the individual HERCULES and TITAN trials also affect the integrated analysis (refer to the Clinical Review Report for the Reimbursement Review submission of caplacizumab in 2020 for details, including the executive summary reproduced in the appendices). In particular, the clinical experts consulted

by CADTH for this review were concerned that the higher proportion of patients in the placebo arm of the integrated population with recurrent rather than initial aTTP may have contributed to poorer outcomes, including higher mortality. In addition, there were several notable differences between the TITAN and HERCULES studies, including the time they were conducted (2010 to 2014 versus 2015 to 2017, respectively) and the administration of caplacizumab (requirement for 1 prior PE session in the HERCULES study and the possibility to extend treatment beyond the first 30 days after PE in the HERCULES study). Thus, the clinical experts consulted by CADTH for this review relayed their uncertainty that the data from the 2 studies could be naively pooled. Statistical analyses of integrated data in the study by Peyvandi et al. (2021) were post hoc, not adjusted for multiple comparisons, and should be interpreted in a descriptive and exploratory fashion.

## Real-World Evidence

### *Description of Studies*

Three studies of 2 RWE cohorts of patients treated with caplacizumab from France and the UK are summarized in this report. The RWE studies provided additional supportive evidence regarding the clinically important outcomes of mortality, health care use, and refractory aTTP, but did not address organ damage or long-term aTTP recurrence.

Coppo et al. (2021) prospectively analyzed outcome data for 90 patients from France with aTTP who were treated from September 2018 to December 2019 with a frontline triplet regimen consisting of PE, immunosuppression with corticosteroids and rituximab, and caplacizumab. Outcomes were compared with 180 historical control patients from the Centre National de Référence sur les Microangiopathies Thrombotiques (CNR-MAT) registry who were treated from June 2015 to September 2018 with standard frontline therapy (PE plus corticosteroids with rituximab as salvage therapy). [REDACTED]

Dutt et al. (2021) conducted a retrospective analysis of data from 85 patients with aTTP (including 4 children) who received caplacizumab in 22 UK hospitals from May 2018 and January 2020. Outcomes for these patients were compared with data from the HERCULES study and to a group of historical control patients consisting of 39 consecutive cases from the UK TTP registry who received standard treatment (PE plus immunosuppression with corticosteroids and rituximab) from 2014 to 2018.

### *Efficacy Results*

In the RWE cohort of the analysis by Coppo et al. (2021), the percentage of patients who received the triplet regimen including caplacizumab who had the composite primary outcome including death and refractoriness was 2.2% versus 12.2% for historical controls (HR = 6.2; 95% CI, 1.4 to 26.3). One patient (1.1%) treated with the triplet regimen died compared with 12 (6.7%) historical controls. One patient (1.1%) treated with the triplet regimen experienced refractory aTTP compared with 16 (18%) historical controls. Compared with historical controls, patients receiving the triplet regimen had numerically fewer PE sessions (triplet regimen: median = 5 sessions; historical control: median = 10 sessions), required numerically lower overall PE volume until remission (triplet regimen: median = 24.2 L; historical control: median = 44.2 L), and had numerically shorter duration of hospitalization (triplet regimen: median = 13 days; historical control: median = 22 days).



In the RWE cohort of the analysis by Dutt et al. (2021), 5 patients (6%) in the caplacizumab cohort died; no deaths were reported among historical control patients. aTTP recurrence and refractoriness were not compared between the 2 groups. In 4 of the patients who died, caplacizumab was introduced more than 48 hours after PE initiation (range, 3 to 21 days). Compared with historical controls, patients who received caplacizumab had numerically shorter duration of PE (triplet regimen: median = 7 days; historical control: median = 9 days) and numerically shorter time from PE initiation to platelet count normalization (triplet regimen: median = 4 days; historical control: median = 6 days). Duration of hospitalization was similar in the caplacizumab cohort (median = 12 days) and the historical control cohort (median = 14 days).

### ***Harms Results***

The safety data for the RWE cohorts were generally consistent with the clinical trial data from the HERCULES study. Bleeding events occurred in 12% to 18% of patients. In the RWE cohort in the analysis by Dutt et al. (2021), 5 patients (5.9%) experienced venous thromboembolism.

### ***Critical Appraisal***

Comparisons between the RWE cohorts and historical controls or the HERCULES trial populations were limited by risk of bias in selection of participants and potential for confounding by measured and unmeasured variables, including nonoverlapping time frames and differences in treatment, primarily use of rituximab, which was used more often in the RWE cohorts. The effect of bias in the selection of patients into the RWE cohorts and the selection of the historical control groups could not be evaluated and contributed to a high level of uncertainty. Except for the reanalysis of the study by Sanofi and Cemka (2021), all comparisons were naive and did not take into account baseline differences between populations, such as cardiac and organ involvement. The rationale for statistical hypothesis testing was not provided, and it was unclear whether statistical tests were prespecified or conducted post hoc for some outcomes. Statistical tests were not adjusted for multiple comparisons and should be interpreted in a descriptive and exploratory fashion.

Generalizability of the RWE to Canadian clinical practice was limited by high rates of rituximab use, including as upfront therapy. In addition, in the RWE cohort of the analysis by Coppo et al. (2021), caplacizumab was administered upfront only, which may not be consistent with the anticipated use of the drug in Canadian clinical practice according to the clinical experts consulted for this review. In the RWE cohort of the analysis by Dutt et al. (2021), the baseline characteristics suggested that some had severe disease and/or multiorgan involvement and may have been candidates for upfront therapy with caplacizumab in Canadian practice; however, in approximately half of patients, caplacizumab was started 2 days or more after PE initiation. In the RWE cohort of the analysis by Dutt et al. (2021), administration of caplacizumab was not aligned with the HERCULES study or the product monograph due to high rates of discontinuation before 30 days after PE.

## Economic Evidence

**Table 1: Cost and Cost-Effectiveness**

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree followed by Markov model
Target population	Adults experiencing an acute aTTP episode
Treatment	Caplacizumab, 11 mg IV injection before PE followed by 11 mg SC on day 1, then 11 mg SC daily after PE, then 11 mg SC daily for 30 days after the last daily PE in addition to SOC. If after the initial treatment course, signs of persistent underlying disease such as suppressed ADAMTS13 activity levels remain present, treatment may be extended for a maximum of 28 days.
Dose regimen	Day 1: 11 mg by IV injection at least 15 minutes before PE followed by 11 mg by SC injection after completion of PE. Subsequent days: <ul style="list-style-type: none"> <li>for duration of PE: 11 mg daily following PE administration</li> <li>post-PE: 11 mg daily for 30 days.</li> </ul> Treatment may be extended for a maximum of 28 days if signs of persistent underlying disease remain present.
Submitted price	Caplacizumab, 11 mg, powder for solution: \$6,200.0000 per single-use vial
Treatment costs	\$223,200 per single aTTP event (assuming medium duration of therapy as per HERCULES trial) <sup>a</sup>
Comparator	SoC, defined as PE continuing for at least 2 days after platelet count reaches $\geq 150 \times 10^9/L$ , corticosteroid treatment of at least 1 mg/kg per day continuing for 1 week after end of PE, and rituximab as permitted by standard practice at each study centre.
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	Lifetime (53 years)
Key data source	HERCULES trial, post-HERCULES study
Key limitations	<ul style="list-style-type: none"> <li>The long-term probability of relapse is highly uncertain. Evidence from the 3-year post-HERCULES study was used by the sponsor to assume that treatment with caplacizumab for a single aTTP event would convey a lifelong benefit in terms of the risk of relapse when compared with SOC. However, results from this study were exploratory only and are thus uncertain in the short term, while the lifetime extrapolation of the reduction in relative risk was not considered plausible in CADTH-obtained clinical expert feedback.</li> <li>The sponsor used a “payoff” approach that was inflexible because it did not allow the recurrence of multiple relapses and oversimplified the modelling of long-term sequelae. Furthermore, the use of prevalence data to estimate long-term sequelae after an individual aTTP event would overestimate the impact of treatment. Together, these increase the uncertainty in the long-term estimates produced by the model.</li> <li>The assumed duration of neuropsychological impairment is unlikely to be lifelong because patients would be expected to have improvement or resolution of such symptoms over time.</li> <li>The relative risk of long-term sequelae for caplacizumab compared with SOC is highly uncertain and modelled results were sensitive to the range of plausible values tested by CADTH.</li> <li>Poor modelling practices were employed limiting thorough validation of the submitted model. This limits the degree of confidence in the model results.</li> </ul>

Component	Description
<b>CADTH reanalysis results</b>	<ul style="list-style-type: none"> <li>In CADTH reanalyses, the reduction in the risk of relapse associated with caplacizumab was limited to 3 years, and the duration of neuropsychological impairment was limited to 1 year.</li> <li>CADTH reanalyses resulted in an ICER of \$269,158 per QALY (incremental costs: \$278,078; incremental QALYs: 1.03). A price reduction of 75% would be required to achieve a threshold of \$50,000 per QALY.</li> <li>CADTH was unable to fully address the lack of data regarding the potential reduction in risk of long-term sequelae and, due to inflexibility in the sponsor’s submitted model, was unable to explore the effect of treatment on multiple relapses or consider incidence-based rates of long-term sequelae. Together, these issues increase uncertainty in the long-term model extrapolations where the majority of incremental QALYs were gained.</li> </ul>

ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aTTP = acquired thrombotic thrombocytopenic purpura; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SC = subcutaneous; SOC = standard of care.

\*Based on the median duration of caplacizumab therapy of 35 days in the HERCULES trial (i.e., the median 5 days of PE therapy plus an additional 30 days).

### Budget Impact

CADTH identified the following key limitations with the sponsor’s budget impact analysis: uncertainties in the annual number of aTTP events and the proportion of caplacizumab use that would be publicly funded and the uptake of caplacizumab. Furthermore, SOC and downstream cost offsets were not considered for either the drug plan or health care system payer perspective. CADTH was unable to address these limitations but made 2 minor corrections to the sponsor’s budget impact analysis model on the annual rate of aTTP events as well as updating Non-Insured Health Benefits (NIHB) population data. In the corrected base-case, the 3-year budget impact of reimbursing caplacizumab is \$24,925,736 (\$6,870,366 in year 1, \$8,294,254 in year 2, and \$9,761,116 in year 3). Scenario analysis to explore the sensitivity of the budget impact model to the limitations noted previously found that the 3-year total budget impact estimates may range from \$19,085,852 to \$42,008,193.

### Request for Reconsideration

The sponsor filed a Request for Reconsideration for the draft recommendation for caplacizumab for the treatment of adults with aTTP in combination with PE and IST. In their request, the sponsor identified the following issues:

- The recommendation should be based on the quality and totality of the submitted evidence for caplacizumab in the context of a rare disease such as aTTP.
- The findings of the post-HERCULES study and the validity of the aTTP recurrence data are supported by the totality of the evidence submitted and is aligned with the insight provided by CADTH’s own clinical experts.
- The importance of the results (particularly the statistically significant mortality benefit) in a larger patient sample and low risk of bias associated with pooling data from the HERCULES and TITAN studies in the context of a rare disease warrants reconsideration of the integrated analysis by CDEC.
- CDEC should re-evaluate the evidence provided by all the RWE studies submitted in the proper context of the value that RWE brings for a rare disease, as stated in CADTH’s own RWE Primer and

considering the principles of “Significant Unmet Need and Uncertainty of Clinical Benefit” as per CADTH’s own Procedures.

- CDEC should reconsider the role of rituximab and characterization of its use as a confounding factor in the evaluation of the clinical evidence because CDEC’s conclusion is not supported by the submitted evidence or aligned with feedback provided by CADTH clinical experts.
- CDEC should consider the evidence for caplacizumab’s role in reducing volume and duration of PE and other measures of health resource utilization (e.g., hospital and intensive care unit stays).
- Further consultation with clinical experts across Canada with direct experience in managing aTTP is proposed to define the most appropriate place in therapy for caplacizumab in Canadian clinical practice that is based on the totality of the clinical evidence.

In the meeting to discuss the sponsor’s Request for Reconsideration, CDEC considered the following information:

- feedback from the sponsor
- information from the initial submission relating to the issues identified by the sponsor
- information from the 2020 submission of caplacizumab
- feedback from 1 clinical specialist with expertise in the diagnosis and management of patients with aTTP
- feedback from the public drug plans
- feedback from 1 clinician group: Canadian Association of Apheresis Nurses
- feedback from 2 patient groups: Answering TTP (Thrombotic Thrombocytopenic Purpura) Foundation, Network of Rare Blood Disorder Organizations.

All stakeholder feedback received in response to the draft recommendation from clinician groups and the public drug programs is available on the CADTH website.

## CDEC Information

### Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunskey, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Mr. Morris Joseph Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

**Initial meeting date: October 26, 2022**

**Regrets: None**

**Conflicts of interest: None**

**Reconsideration meeting date: March 24, 2023**



**Regrets:** One expert committee member did not attend

**Conflicts of interest:** None