CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

CAPLACIZUMAB (CABLIVI)

(Sanofi Genzyme, a division of Sanofi-Aventis Canada Inc.)

Indication: Indicated for the treatment of adults with acquired thrombotic thrombocytopenic purpura (aTTP) in combination with plasma exchange (PEX) and immunosuppressive therapy

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Abbreviations

ADAMTS13	a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
aTTP	acquired thrombotic thrombocytopenic purpura
CDR	CADTH Common Drug Review
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
PEX	plasma exchange therapy
QALY	quality-adjusted life-year
RR	relative risk
SOC	standard of care
TTP	thrombotic thrombocytopenic purpura
WTP	willingness to pay

Table 1: Summary of the Sponsor's Economic Submission

Drug product	Caplacizumab (Cablivi)
Study question	What is the cost-effectiveness of caplacizumab in addition to standard of care (SOC) compared with SOC alone for the treatment of adults with acquired thrombotic thrombocytopenic purpura (aTTP)?
Type of economic evaluation	Cost-utility analysis
Target population	Adults experiencing an acute aTTP episode
Treatment	Caplacizumab 11 mg IV prior to PEX followed by 11 mg SC afterward on day 1, and 11 mg SC daily for the remainder of daily PEX therapy, then for 30 days afterward, in addition to SOC.
Outcome	QALYs
Comparator	SOC, defined as PEX continuing for at least 2 days after platelet count reaches ≥ 150 × 10^9/L, corticosteroid treatment of at least 1 mg/kg per day IV or orally continuing for one week after PEX is ended, and rituximab as permitted by standard practice at each study centre.
Perspective	Canadian public health care payer
Time horizon	Lifetime (up to 60 years)
Results for base case	ICER = $72,786 per QALY
Key limitations	• The sponsor considered only a single episode of aTTP in its analysis, which is inconsistent with many patients' experiences with aTTP recurrences over the long term. • The relative risk of mortality during an acute aTTP episode was inappropriately modelled, inflating the survival benefit of caplacizumab plus SOC relative to SOC alone. In addition, not all deaths within the HERCULES trial for caplacizumab were accounted for in the economic model. • Relapses of aTTP occurring after 30 days post-PEX in the HERCULES trial were not included in the submitted model, despite occurring within the follow-up time modelled in the first cycle (three months). The CADTH Clinical Review noted that a proportion of patients had an aTTP relapse immediately after cessation of caplacizumab therapy. • The sponsor assumed the mortality rate for patients in remission was identical to the general population. Long-term observational studies report that patients' mortality following an aTTP event is higher than that of a general population, indicating that overall mortality was underestimated. • The health utility score for patients in remission without stroke or MI was based on utility weights for the general population from the UK. This likely overestimated the utility weights of patients in remission and may not be generalizable to the Canadian setting. • Uncertainty associated with the relative risk of death, MI, and stroke during the aTTP episode was underestimated, as an arbitrary coefficient of variation was assumed.

CADTH estimate(s)	CADTH's base case included all deaths and aTTP recurrences reported in the caplacizumab arm of the HERCULES trial; revised mortality rate for patients in remission, to be consistent with clinical literature; Canadian utility data and reduced health utility scores in the remission states; and revised uncertainty estimates for relative risk parameters to reflect the underlying trial data. CADTH was unable to address structural limitations regarding subsequent aTTP recurrences. Based on the CADTH reanalysis, treatment with caplacizumab in addition to SOC was associated with an ICER of $237,053 per QALY compared with SOC alone. In order for caplacizumab plus SOC to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY, the submitted price would need to be reduced by approximately 75%.

aTTP = acquired thrombotic thrombocytopenic purpura; ICER = incremental cost-effectiveness ratio; MI = myocardial infarction; PEX = plasma exchange therapy; QALY = quality-adjusted life-year; SC = subcutaneous; SOC = standard of care.

Drug	Caplacizumab (Cablivi)
Indication	Indicated for the treatment of adults with acquired thrombotic thrombocytopenic purpura (aTTP) in combination with plasma exchange (PEX) and immunosuppressive therapy
Reimbursement request	As per indication
Dosage form(s)	Powder for solution (11 mg)
NOC date	February 28, 2020
Sponsor	Sanofi Genzyme, a division of Sanofi-Aventis Canada Inc.

Executive Summary

Background

Caplacizumab (Cablivi) is a selective bivalent anti-von Willebrand factor nanobody indicated for the treatment of adults with acquired thrombotic thrombocytopenic purpura (aTTP) in combination with plasma exchange (PEX) and immunosuppressive therapy.[1] Caplacizumab is available in single or multi-pack kits (seven administrations) containing an 11 mg vial of caplacizumab powder, a pre-filled syringe of sterile water for injection, a vial adaptor, a needle, and two alcohol swabs. The recommended loading dose for caplacizumab is 11 mg by IV injection at least 15 minutes prior to PEX, followed by an 11 mg subcutaneous injection after completion of PEX on that day. Subsequently, 11 mg of caplacizumab should be administered as a daily maintenance dose by subcutaneous injection following PEX administration for the duration of daily PEX therapy, then once daily for 30 days following the last daily PEX treatment. If, after the initial treatment course, signs of persistent underlying disease such as suppressed a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activity levels remain present, treatment may be extended for a maximum of 28 days. No data on re-treatment with caplacizumab are available.[1] At the submitted price of $6,200 per 11 mg dose[2] and assuming [redacted] days of therapy (i.e., mean exposure to caplacizumab for patients in the active treatment group of the HERCULES trial; the reported maximum was 65 days),[3] the cost of caplacizumab for an aTTP episode is $[redacted] per patient (maximum: $409,200).

The sponsor submitted a cost-utility analysis[4] comparing caplacizumab in addition to standard of care (SOC) with SOC alone in adult patients with aTTP from the perspective of a Canadian public health care payer. SOC consisted of: PEX, a corticosteroid regimen of three days of IV prednisolone followed by oral prednisone for the duration of daily PEX and for a week afterward, and the option of other immunosuppressant therapy such as rituximab. The analysis was conducted over a lifetime time horizon (60 years) with cycle length defined as three months; future costs and benefits were discounted at 1.5% per annum. Patients entered the model in an acute aTTP state (Figure 1). During this first cycle, patients could experience events with long-term consequences, such as myocardial infarction, stroke, or death. Patients could also experience other adverse events, such as a PEX complication (i.e., infection, treatment-related serious bleeding, pulmonary embolism, or deep vein thrombosis) and be at risk of exacerbation within this first cycle, defined as a platelet count drop after initial normalization requiring the re-initiation of daily PEX within 30 days of stopping it. The relative risks (RRs) of these events in the caplacizumab group were derived from the HERCULES trial,[3] while the underlying probability of each event occurring in the

SOC arm was from a variety of sources.[3,5-7] Following the first cycle, patients who remained alive transitioned to the remission phase in either a chronic myocardial infarction or chronic stroke health state if they had an MI or stroke, respectively, or otherwise in a "no neurologic or cardiac condition" health state. As the analysis modelled only a single aTTP event, patients then stayed in their respective remission states until death. These health states were associated with different costs, utilities, and mortality risks, with patients in the "no neurologic or cardiac condition" remission health state having mortality rates and utility scores consistent with the general population. Patients were assigned utility scores from a UK EuroQol 5-Dimensions (EQ-5D) study of the general population published in 1999,[8] with a disutility for an acute aTTP episode applied additively based on the length of the hospital stay of the acute or exacerbation aTTP event, as observed in the HERCULES trial,[3] and an acute and chronic utility multiplier for MI or stroke events.[9] Costs included hospitalization in the intensive care unit (ICU) and general ward, acquisition and administration of PEX, acquisition of caplacizumab and other pharmacotherapies (i.e., prednisolone, prednisone, and rituximab), laboratory testing, and specialist visits.[10-13]

In the base case, the sponsor reported that caplacizumab in addition to SOC was associated with an incremental cost-effectiveness ratio (ICER) of $72,786 per quality-adjusted life-year (QALY) compared with SOC alone. At a willingness-to-pay (WTP) threshold of $50,000 per QALY, the probability of caplacizumab being cost-effective under the sponsor's analysis was 12.5%.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified a number of key limitations with the model submitted by the sponsor. The model considered only a single episode of aTTP, whereas it is often a recurrent condition. The RR of mortality in the first cycle was inappropriately modelled, inflating the survival benefit of caplacizumab compared with what was observed in the clinical trial. Mortality was based on a naive comparison informed by a systematic review commissioned by the sponsor for the SOC arm and by the HERCULES trial for the caplacizumab arm. Furthermore, the sponsor excluded an aTTP-related death in the caplacizumab arm that was observed during the follow-up period of the HERCULES trial. Relapses occurring after 30 days post–daily PEX in the HERCULES trial were not included in the economic model, despite being otherwise identically defined as exacerbations; these relapses would be expected to occur within the time period of the first cycle of the model.

Furthermore, the majority of the QALY gain occurred during the extrapolated remission phase and assumptions around the quality and quantity of life experienced by aTTP patients in remission were identified to be key drivers of the model. The mortality rate for patients in remission without a history of MI or stroke was assumed to be equivalent to that of the general population. This is not aligned with evidence in the literature, which indicates that patients with aTTP have substantially higher mortality and frequency of comorbidities than those in the general population.[14] Additionally, patients in remission were assumed to have utility scores equivalent to the general population in the UK, despite these patients having more comorbidities and living with other stresses associated with a history of aTTP, as per the patient input collected by CADTH, when compared with the general population. Furthermore, the selection of a UK source may be less generalizable to the Canadian setting. Together, these two limitations would underestimate mortality and overestimate the expected QALYs for those who survive the acute aTTP episode, with a greater bias favouring caplacizumab plus SOC.

Finally, uncertainty in the RR of long-term consequences (death, MI, stroke) was underestimated by using an assumption of a 15% standard error around the mean rather than deriving the statistical distribution from the trial results.

CADTH attempted to address most of these issues. The CADTH base-case analysis incorporated all deaths and recurrences in the caplacizumab arm of the HERCULES trial to re-estimate the RRs for caplacizumab in addition to SOC, increased the mortality rate for patients in remission based on the rates reported in an observational study, incorporated more recent Canadian utility scores and further incorporated a utility modifier to reflect the reduced quality of life of patients with chronic conditions, and captured the uncertainty inherent in the HERCULES trial for certain RR parameters. CADTH was unable to address the recurrent nature of aTTP and the potential costs and benefits when using caplacizumab for future aTTP episodes. In CADTH's revised base-case analysis, the ICER associated with the use of caplacizumab in addition to SOC compared with SOC alone was $237,053 per QALY.

Conclusions

In adult patients with aTTP, the use of caplacizumab in addition to SOC reduced the frequency of aTTP recurrence within the active treatment and follow-up periods of the HERCULES trial and was associated with one patient death within the same time period, compared with three deaths in patients treated with SOC alone. This possible difference in mortality is a key driver in the economic analysis.

CADTH's base-case reanalysis concluded that, at the submitted price, the addition of caplacizumab to SOC was associated with an ICER of $237,053 per QALY compared with SOC alone. At a WTP of $50,000 per QALY, the price of caplacizumab would need to be reduced by approximately 75% to be considered cost-effective.

CADTH was unable to consider future aTTP episodes, specifically, the potential impact of caplacizumab treatment on reducing or delaying them, or the costs associated with further treatment for acute episodes. Additionally, the vast majority of incremental QALYs gained within the model occurred during the extrapolated remission period rather than during the acute phase for which data exists. As such, assumptions around the quantity and quality of life experienced by patients who survive an aTTP episode are key drivers of the cost-effectiveness results. With little data available regarding these outcomes, the resulting ICER is uncertain.

Information on the Pharmacoeconomic Submission

Summary of the Sponsor's Pharmacoeconomic Submission

The sponsor submitted a cost-utility analysis[15] comparing caplacizumab plus SOC to SOC alone in adult patients with aTTP. As outlined in the HERCULES clinical trial, SOC consisted of: PEX, a corticosteroid regimen of three days of IV prednisolone followed by oral prednisone for the duration of daily PEX and for a week afterward, and the option of other immunosuppressant therapy such as rituximab if deemed necessary (i.e., 25% of patients in the model were assumed to receive four once-weekly rituximab treatments based on physician opinion). Patients in the caplacizumab group received 11 mg of caplacizumab by IV injection prior to PEX, followed by an 11 mg subcutaneous injection after completion of PEX on the first day, then 11 mg subcutaneous per day for the duration of PEX therapy and for at least 30 days following the last daily PEX. In cases where underlying disease remained evident, patients could receive up to four weekly extensions to caplacizumab therapy on an open-label basis. Based on the HERCULES trial, the mean duration of treatment with caplacizumab was [redacted] days, with a reported range of 1 to 65 days. A probabilistic Markov state–transition model was submitted that considered a lifetime time horizon from the perspective of a Canadian public health care payer with a cycle length of three months. An annual discount rate of 1.5% was applied to both costs and clinical outcomes, with half-cycle correction applied.

Patients entered the model in an acute aTTP state, which captured the first three months after the onset of an aTTP episode (Appendix 5, Figure 1). During this first cycle, patients could experience events with long-term consequences, such as an MI, a stroke, or death. Regardless of neurological or cardiac consequences, patients could also experience other adverse events, such as PEX-related complications (e.g., infection), serious bleeding, or a major thromboembolic event (i.e., pulmonary embolism or deep vein thrombosis). Patients were also at risk of exacerbation within this first cycle, defined as a drop in platelet count to below 150×10^9/L after initial recovery, requiring the re-initiation of daily PEX within 30 days of stopping it. The RRs for these events in the caplacizumab group were derived from the HERCULES trial,[3,6] while the underlying probability of each event occurring in the SOC arm was from a variety of sources, including an unpublished meta-analysis conducted by the sponsor,[5] a published database study,[7] and the HERCULES trial (Appendix 5, Table 12).[3,6]

Following the first cycle that captured the acute phase, patients transitioned to the remission phase for subsequent cycles. Patients who remained alive in the acute phase transitioned to the "no neurologic or cardiac condition" health state if they had not suffered an MI or stroke during the acute aTTP phase, or to "chronic MI," or "chronic stroke" if they had experienced an MI or stroke during the acute aTTP phase, respectively. As the analysis modelled only a single aTTP event, patients then stayed in their respective remission states until death. These health states were associated with differing costs, qualities of life, and mortality risks.

Patients were assigned baseline gender- and age-specific utilities from a UK EQ-5D study.[8] The disutility for an acute aTTP episode (-0.230), whether initial or exacerbation, was derived using sickle cell anemia as a proxy[16] and applied additively for the length of the hospital stay of the acute aTTP event or exacerbation. Patients could also experience other adverse events that were incorporated additively as disutilities into the model (Appendix 5, Table 12). Additionally, patients who experienced an MI or stroke had an acute utility multiplier

modifying their utility weight during the first cycle, and a chronic utility multiplier modifying their utility weight thereafter (Appendix 5, Table 12).

Costs during the acute phase included hospitalization in the ICU and general ward, acquisition and administration of PEX, acquisition of caplacizumab and other pharmacotherapies (i.e., prednisolone, prednisone, and rituximab), laboratory testing, and hematology specialist visits. Unit costs were sourced from the Canadian Institute for Health Information for hospital days,[10] the sponsor's submitted price for caplacizumab, the Ontario Drug Benefit Formulary[12,17] for other drug costs, the Canadian Blood Services for plasma-acquisition costs, and the Ontario Schedule of Benefits for Physician Services[11] as well as the Schedule of Benefits for Laboratory Services[13] for test, administration, and procedure costs.

Sponsor's Base Case

The sponsor presented a probabilistic base case, where the use of caplacizumab in addition to SOC was associated with an additional 3.07 QALYs per patient over the lifetime time horizon, at an additional cost of $223,408, leading to an ICER of $72,786 per QALY gained compared with SOC alone. At a WTP threshold of $50,000 per QALY, caplacizumab was cost-effective in 12.5% of simulations. Deterministic results reporting the cost per life-year gained can be found in Appendix 5, Table 15.

A breakdown of the sponsor's costs by category and QALYs by health state can be found in Table 13 and Table 14 in Appendix 5, respectively. The key cost difference was drug-acquisition costs, while QALY gains predominantly occurred in the extrapolated remission portion of the model as a result of increased survival modelled during the initial aTTP episode for patients in the caplacizumab plus SOC group.

Table 2: Summary of the Results of the Sponsor's Base Case

	Total costs ($)	Incremental cost of caplacizumab ($)	Total QALYs	Incremental QALYs of caplacizumab	Incremental cost per QALY ($)
SOC	67,546	Reference	18.85	Reference	Reference
Caplacizumab + SOC	290,955	223,408	21.92	3.07	72,786

QALY = quality-adjusted life-year; SOC = standard of care.

Summary of Sponsor's Sensitivity Analyses

The sponsor also conducted a series of probabilistic scenario analyses considering different discount rates (i.e., 0% and 3%) or time horizons (i.e., 20 years, 30 years, and 40 years), adopting a societal perspective (i.e., captured either based on the inclusion of lost productivity for patients while they remained in hospital or were attending physician visits or assuming a month of lost productivity per aTTP event), including an additional ward stay for thromboembolic and adverse events, and applying an added cost for sudden deaths. Of these analyses, the discount rate and the time horizon assumptions had the largest impact on the model's results, with the ICER increasing with a larger discount rate or shorter time horizon.

The sponsor conducted a series of one-way deterministic sensitivity analyses to explore parameter uncertainty within the model. The inputs varied in these deterministic sensitivity analyses were not clearly reported but the sponsor reported that variables with the greatest

impact included: varying the patient's starting age, where younger patients led to lower ICERs, and varying the probability of death from an aTTP event in the SOC arm, where higher probabilities of death in the SOC arm led to lower ICERs.

Limitations of Sponsor's Submission

- **Subsequent aTTP recurrences were not modelled**: The sponsor's model considered a single acute episode of aTTP and its related short-term recurrences (i.e., those happening within one to three months). However, aTTP is often a recurrent disease over the long term, with 43% of patients entering the HERCULES trial presenting with a subsequent aTTP recurrence rather than an initial event.[3] Similarly, a registry study published by Deford et al. in 2013 reported that 37% of Oklahoma patients with clinically diagnosed thrombotic thrombocytopenic purpura (TTP) (ADAMTS13 activity < 10% during first episode) had one to four relapses within the observation period (median of 7.8 years).[14] This was further supported by the patient input submitted to CADTH in which only 21% of patients reported not having had a subsequent aTTP relapse (see Patient Input section that follows). CADTH, like the sponsor, was unable to incorporate relapses beyond the initial cycle, given the model's structure and the lack of data on the impact of treatment on long-term relapse (i.e., beyond three months from the index aTTP event). An aTTP relapse would be associated with further decrements to quality of life as well as increased health care costs in terms of managing the relapse and potential additional caplacizumab therapy. At the time of this review, the sponsor is conducting a follow-up study on patients from the HERCULES trial, including studying the prevalence of aTTP recurrences and subsequent aTTP-related events,[18] which may provide further insight on the impact of caplacizumab on recurrence over time. However, these data were not yet available at the time of this review.
- **The RR of mortality during an acute aTTP episode was inappropriately calculated:** As the number of SOC-treated patients who died during the 30-day post–daily PEX treatment period was low in the HERCULES trial (3 of 73 patients [4.1%]) compared with the mortality rates expected in clinical practice for this population, the probability of death during the acute phase of an aTTP episode for SOC patients in the sponsor's model was based on a meta-analysis of an unpublished systematic review[5] (probability of death = [redacted]%). The meta-analysis value is [redacted] other estimates of mortality that report a 10% to 20% probability of death (see CADTH CDR Clinical Review Report: Disease Background) for patients receiving SOC and aligns with the experience of the clinical experts consulted by CADTH. The sponsor then naively compared the probability of death between treatment arms: 0% of patients receiving caplacizumab during the first 30 days post–daily PEX in HERCULES died (0 of 71 patients) compared with the higher probability reported in the systematic review. This, in effect, more than tripled the survival benefits of caplacizumab compared with what has been observed in the HERCULES trial (i.e., 0% versus [redacted]%, for caplacizumab plus SOC versus SOC alone, respectively [economic model], rather than 0% versus 4.1% [HERCULES trial]). This further ignored the fact that one patient who had received caplacizumab died during the HERCULES follow-up period due to aTTP-related causes and thus should have been included in the model's first cycle (i.e., 90 days).

  CADTH reanalyses incorporated three deaths in the SOC group and one death in the caplacizumab group and preserved the comparison by applying the relevant RR to the probability of death for patients receiving SOC from the sponsor's commissioned systematic review to derive an adjusted mean probability of death of 4.5% for modelled patients receiving caplacizumab in the first cycle (Table 3).

- **Relapses within the HERCULES trial were not modelled:** The sponsor distinguished between aTTP exacerbations and aTTP relapses based on whether the recurrence of thrombocytopenia (return to low platelet counts) occurred within 30 days of stopping daily PEX (which the sponsor defined as an exacerbation), or after 30 days (which the sponsor defined as a relapse). Only exacerbations were included within the model. Although HERCULES reported an exacerbation rate of 38.4% for patients receiving SOC,[3] the sponsor selected an estimate of [redacted]%, based on the pooled frequency of exacerbations within the 30 days post–daily PEX reported in the sponsor's commissioned systematic review. To determine the probability of exacerbation on caplacizumab plus SOC, the sponsor applied the RR of aTTP exacerbation in the caplacizumab plus SOC group (RR = 0.11) reported in the HERCULES trial to the probability of exacerbation in the SOC group to derive a probability of [redacted]% for patients within the caplacizumab group. This RR was calculated based on 3 of 71 patients in the HERCULES trial experiencing an exacerbation. However, by limiting the model to exacerbations only and excluding relapses, the sponsor ignored the direct masking effect caplacizumab has on platelet counts. In fact, six patients in the caplacizumab arm of the HERCULES trial were reported to have relapsed directly after cessation of 30 or more days of caplacizumab treatment after cessation of daily PEX. Given the model's cycle length of 90 days, this time frame should encompass the impact of any exacerbation or relapse noted within the trial. Patients who suffered a relapse would trigger similar costs and quality-of-life decrements as those who suffered an exacerbation, according to the clinical experts consulted on this review. Thus, CADTH reviewers considered the additional six patients in the caplacizumab group who relapsed during the HERCULES trial as equivalent to those who had an exacerbation for the purposes of its reanalysis.
- **Mortality rate in remission was underestimated**: The sponsor assumed that patients who survived their presenting aTTP episode had mortality rates equivalent to an age- and gender-matched general population if they had not had a stroke or MI. Patients who experienced a neurological or cardiac event within their acute aTTP episode were assumed to have a mortality equivalent to that of other survivors of a stroke or MI. Clinical experts consulted by CADTH noted that the assumption that patients who enter remission without experiencing a neurological or cardiac consequence during their acute aTTP event are unlikely to have mortality rates similar to those of the general population. This is supported by a 2013 Oklahoma registry study by Deford et al.[14] that found that surviving an aTTP episode was associated with a higher number of comorbidities compared with the general population, including hypertension, diabetes, systemic lupus erythematosus, and depression. Overall, patients with a history of aTTP had a higher all-cause mortality rate that was 10 times or more that of the general population of Oklahoma or the US as a whole over a median follow-up of 7.8 years (range of 0.3 to 17.1 years).[14] By underestimating mortality for aTTP patients in the remission states of the model, the sponsor's analysis overestimated the QALY benefit associated with caplacizumab plus SOC, as the majority of the QALY gains occurred in the extrapolated remission portion of the model. The CADTH reanalyses adjusted the probability of death for patients in the remission states to reflect the values reported in the literature.
- **Utility weights were inappropriately modelled:** Utility weights were based on a UK EQ-5D study of the general population published in 1999.[8] This study is outdated and does not reflect Canadian tariffs that have since become available; compared with the UK values, the Canadian utility weights tend to be lower for patients under the age of 45 but higher for those over the age of 45.[8,19] The sponsor further assumed that patients who went into remission without suffering a stroke or MI had utility weights equivalent to that of

the general population. As the sponsor's QALY results are driven by QALYs accrued in the "no neurologic or cardiac condition" remission health state (i.e., during the extrapolated period of the model) (Appendix 5, Table 14) in which the main difference between the caplacizumab plus SOC group and the SOC alone group is the proportion of patients who survived the aTTP event, this utility weight magnifies the clinical benefit gained. As stated previously, patients who have had an aTTP episode are more likely to have a number of comorbidities compared with the general population, which would have an impact on quality of life.[14] Additionally, the patient input received by CADTH indicated that aTTP has an impact on quality of life, including increased stress, anxiety, and mood swings, beyond the acute state (i.e., three months).

While utility values for patients with aTTP were not found in the literature, health utilities based on the Health Utilities Index Mark 3 were available from the 2013 and 2014 Canadian Community Health Survey for both the general population[19] and for a number of major chronic conditions.[20] For the base-case reanalysis, CADTH replaced the sponsor's 1999 UK general population utility weights with those elicited in Canada in 2013 and 2014 (reported in 2018). Furthermore, CADTH assumed a utility modifier consistent with that of asthma, the condition with the least severe impact on quality of life as reported in the Canadian Community Health Survey (93% of the utility score of the general population).[20] Given uncertainties about the true utility impact of patients with a history of aTTP, CADTH also explored a more conservative assumption by setting the utility modifiers to be consistent with having a mood disorder (75%) in scenario analyses.

- **Uncertainty in the RRs was underestimated:** Although some inputs within the sponsor's model vary individually by treatment group (i.e., probability of experiencing an exacerbation, probability of deep vein thrombosis) and reflect the uncertainty associated within the HERCULES trial data, others relied on a 15% variation around the mean probability for the SOC group and the RR for the caplacizumab plus SOC group (i.e., death , stroke, and MI). As only a small number of events occurred within the HERCULES trial, which was not powered to detect differences in these outcomes, the RR of these events between treatment groups is highly uncertain. By setting uncertainty arbitrarily as 15% of the mean, the sponsor's model does not accurately reflect the extent of the true uncertainty from the trial. For example, using the sponsor's method where standard error is 15% of the mean, the RR of stroke during an aTTP episode was associated with a range of 0.50 to 0.91, whereas the 95% confidence interval (CI) around the RR calculated using the trial data is [redacted]. Of particular importance is the uncertainty in the RR of death from an aTTP event, as mortality is a key driver of the model. The CADTH reanalyses adjusted the distributions for each parameter to reflect the underlying data set from the HERCULES trial.

CADTH CDR Reanalyses

CADTH incorporated the following changes during reanalysis:

1. Death related to aTTP in the caplacizumab group during the full follow-up period of the HERCULES trial was included in the calculation of the RR of mortality during the acute aTTP episode (i.e., initial three months). The resulting RR of death for caplacizumab compared with SOC (mean RR = 0.34; 95% CI, 0.04 to 3.22) was varied probabilistically through beta distributions based on the number of deaths reported in each treatment group in the HERCULES trial. To prevent extreme draws leading to impossible proportions of patients experiencing an event, the RR was restricted within its 95% CI.

2. All recurrences in the HERCULES trial, either exacerbations or relapses, were included. As the sponsor's commissioned systematic review did not include recurrences that occurred after 30 days post-PEX but within three months (i.e., cycle length of the model), whereas the HERCULES trial reported recurrence for the full length of the trial (i.e., up to 13 weeks), the probability of recurrence from the HERCULES trial was used for each group to ensure consistency.
3. Recent Canadian data were used to inform the average health utility score of the general population by age and gender. A multiplier of 0.93, consistent with asthma, the chronic condition with the least severe impact on utility score as reported in a study using the same dataset, was used to estimate the reduced quality of life associated with patients with a history of aTTP.
4. Mortality in remission was assumed to be 10 times that of the age- and gender-matched general population, based on the 15-year probability of death reported for TTP patients in Deford et al., compared with the same probability for the general Oklahoma and US populations. This calculated per-cycle mortality was limited to a maximum consistent with the similarly converted 15-year probability of death in Deford et al.,[14] after the removal of a patient in the study who appeared to have died during their acute aTTP event or shortly thereafter, as such death would have already occurred within the acute cycle of the model. The increased mortality risks associated with a history of MI and stroke were removed (i.e., multipliers set to 1) to prevent double-counting of aTTP-related causes of death. Once the probability of death per cycle of the general population exceeded that of these assumptions (at age 76), the general population probability was used.
5. The RRs of patients experiencing an MI or stroke were varied probabilistically through beta distributions based on the number of events reported in each treatment group in the HERCULES trial rather than by setting uncertainty to be arbitrarily at 15% of its mean value. To prevent extreme draws, the RR was restricted to its 95% CI.

In addition, CADTH identified the following minor errors that were also adjusted:

1. Correction of minor errors in the model: The cost of X-rays and bone marrow biopsies for patients receiving caplacizumab was overstated and, as the submitted price of caplacizumab is not associated with uncertainty, probabilistic variation around the submitted price was removed.

In CADTH's base-case reanalysis, the addition of caplacizumab to SOC was associated with a gain of 1.04 QALYs at an additional cost of $246,568, resulting in an ICER of $237,053 per QALY gained when compared with SOC alone (Table 3). At a WTP of $50,000 per QALY, the probability that caplacizumab plus SOC is cost-effective compared with SOC alone is 0%, rising to 5% at a WTP of $100,000 per QALY.

Table 3: CDR Base-Case Reanalyses

	Description	Sponsor's base-case value	CADTH value	Incremental cost ($)	Incremental QALYs	ICER ($/QALY)
	Sponsor's base case	**Reference**		**223,408**	**3.07**	**72,786**
1	All HERCULES deaths included (with uncertainty reflecting the trial data) for the acute aTTP episode	• Probability of death for caplacizumab): 0% (calculated based on RR = 0.00) • Uncertainty assumed to be 15% of mean estimate	• Probability of death for caplacizumab: [redacted]% (calculated based on mean RR = 0.34) • Uncertainty modelled using beta distributions based on trial data for each group; calculated RR limited to 95% CI	221,924	1.65	134,511
2	All recurrences in trial included	• Probability of recurrence for SOC: [redacted]% • Probability of recurrence for caplacizumab: [redacted]% (calculated, based on RR = [redacted])	• Probability of recurrence for SOC: 38.4% • Probability of recurrence for caplacizumab: 12.7% (calculated based on RR = 0.33)	244,604	3.08	79,367
3	Mortality rate in remission	• Assumed equivalent to general population • SMR (post-MI): 2.02 • SMR (post-stroke): 3.90	• Assumed 10 times higher than general population based on 15-year probability of death reported in Deford (2013); equal to general population once it surpasses Deford • SMR (post-MI): 1.00 • SMR (post-stroke): 1.00	221,581	2.49	88,847
4	Utility weights	• General population based on UK value set, reported in 1999[8] • Multiplier (in remission): 1.00	• General population based on Canadian value set, reported 2018[19] • Multiplier (in remission): 0.93[20]	223,262	2.91	76,816
5	Stroke and MI uncertainty reflecting the trial data	Uncertainty modelled by 15% assumption	Uncertainty modelled using beta distributions based on trial data for each group, calculated RR limited to 95% CI	220,766	2.88	76,570
6	Cost errors corrected; price of caplacizumab certain	• Cost of X-ray, caplacizumab patients: $52	• Cost of X-ray, caplacizumab patients: $43 • Cost of bone marrow biopsy,	222,914	3.07	72,565

	Description	Sponsor's base-case value	CADTH value	Incremental cost ($)	Incremental QALYs	ICER ($/QALY)
		• Cost of bone marrow biopsy, caplacizumab patients: $264 • Price of caplacizumab: probabilistic	caplacizumab patients: $78 • Price of caplacizumab: deterministic			
1 to 6	**CADTH base case**			**246,568**	**1.04**	**237,053**

CDR = CADTH Common Drug Review; CI = confidence interval; ICER = incremental cost-effectiveness ratio; MI = myocardial infarction; QALY = quality-adjusted life-year; RR = relative risk; SMR = standardized mortality ratio; SOC = standard of care.

Of these CADTH step-wise reanalyses, the majority impact was on the sponsor's conclusions on the number of QALYs patients would gain as a result of treatment with caplacizumab and SOC. Similar to the sponsor's results, the majority of the incremental QALYs gained occurred in the extrapolated remission phase. As previously noted, most of the incremental QALY gain associated with the use of caplacizumab was due to the increased survival modelled for patients who received caplacizumab during the acute period of their aTTP episode within the HERCULES trial; the magnitude of this gain further relies on assumptions regarding surviving patients' extrapolated quantity and quality of life after the trial. Additionally, due to the size of the HERCULES trial, and the low event rate of major drivers within the economic model (patient death during the aTTP episode as well as MI and stroke events), there is a high degree of uncertainty in the RR of these events between caplacizumab plus SOC and SOC alone.

CADTH conducted a series of scenario analyses to explore uncertainties in the base-case assumption, including: assuming a health utility score modifier consistent with having a mood disorder rather than asthma for patients in remission; assuming a probability of death during the first cycle for patients in the SOC group consistent with that observed in the HERCULES trial rather than the probability from the sponsor's systematic review (i.e., 1.4% and 4.1% for the caplacizumab plus SOC and SOC alone treatment groups, respectively, versus [redacted]% and [redacted]% in the CADTH base-case analysis); and including societal costs in the form of lost productivity for patients during aTTP episodes and due to long-term monitoring in response to the patient input received regarding the impact of aTTP. Of these, assuming a probability of death during the acute aTTP episode consistent with that observed in the HERCULES trial had the largest impact on the ICER, fewer patients dying while receiving SOC would lead to fewer opportunities for caplacizumab to improve survival and, thus, the ICER is much higher ($1,195,347 per QALY) (Appendix 5, Table 18).

CADTH conducted a price-reduction analysis using the sponsor's and CADTH's base-case analyses (Table 4). Based on the CADTH base-case reanalyses, the price of caplacizumab would need to be reduced by approximately 55% or 75% to be considered cost-effective at WTP thresholds of $100,000 and $50,000 per QALY, respectively.

Of note, CADTH was unable to address the long-term impact of treatment with caplacizumab on later recurrences of aTTP and overall patient quality of life, as limited data were available at the time of this review.

Table 4: CDR Reanalysis Price-Reduction Scenarios

ICERs of caplacizumab plus SOC compared with SOC alone		
Price	**Base-case analysis submitted by sponsor[a] ($)**	**CADTH base-case analysis ($)**
Submitted	72,565	237,053
10% reduction	64,989	216,761
20% reduction	57,220	184,620
30% reduction	48,717	161,870
40% reduction	41,379	139,475
50% reduction	33,673	115,088
60% reduction	25,723	89,490
70% reduction	18,035	63,389
80% reduction	10,105	37,536

CDR = CADTH Common Drug Review; ICER = incremental cost-effectiveness ratio; SOC = standard of care.

[a] CADTH reanalysis 1 (i.e., the sponsor's base case, but with cost corrections and a deterministic cost for caplacizumab).

Issues for Consideration

Rituximab usage: According to the clinical experts consulted by CADTH, rituximab is used less often for the treatment of aTTP in Canadian practice than reported in the HERCULES trial (43%) or assumed within the sponsor's model (25%), often due to access limitations. The impact of this difference on modelled morbidity, mortality, PEX treatment, and length of hospital stay is unknown. Rituximab has been associated with shorter hospital stays as well as fewer and later relapses,[21] and has been used pre-emptively to prevent relapse in patients in remission with severe ADAMTS13 deficiency.[22] See Appendix 1 for the costs associated with standard adjunctive rituximab therapy for aTTP.

PEX therapy: CADTH was unable to independently confirm the unit cost of blood products for infusion and thus the cost of PEX therapy. CADTH therefore assumed the same price used by the sponsor in its model for PEX therapy (Appendix 1, .

Table 6). If the daily cost of blood products used is substantially different than assumed, the incremental cost of caplacizumab therapy may change, as caplacizumab was associated in the model with a decreased length of PEX therapy. See Appendix 5, Table 18 for sensitivity analyses assuming higher and lower unit costs for plasma products used for PEX therapy.

Development of anti-drug antibodies: Anti-drug antibodies were detected in three caplacizumab patients (9%) in the TITAN trial[23] and two caplacizumab patients (2.8%) and one placebo patient (1.4%, presumably during open-label caplacizumab treatment) in the HERCULES trial. No serious adverse events were reported for these patients, and no impact on drug efficacy was observed.[3] The potential impact of developing anti-drug antibodies was not considered in the economic analysis.

Outpatient transition: Caplacizumab is initiated in hospital and continued in an outpatient setting. The transition from hospital budgets to drug plan budgets, as well as the potential offset of costs due to the reduced length of stays in the ICU and in hospital overall, may be seen by hospital budget holders; however, drug plan payers would not benefit from these potential offsets, which may complicate the implementation of caplacizumab therapy.

Therapy decisions: According to the clinical experts consulted by CADTH, tapering and stopping PEX therapy, as well as reinitiating it in the case of recurrence, is often guided in part by normalization or worsening of platelet count, a response measure that may be

masked by caplacizumab. Caplacizumab raises platelet count without necessarily resolving the underlying condition, and this artificial rise in platelets may complicate treatment decisions and patient monitoring, as well as potentially delay some exacerbations rather than prevent them. The HERCULES trial administered caplacizumab for the length of daily PEX therapy and for an additional 30 days, with the option of up to four weeks of additional caplacizumab guided by risk factors for recurrence such as persistent, severe ADAMTS13 deficiency.[3] The product monograph states: "Patients, especially those with ADAMTS13 activity < 10% at or near the time of discontinuation of Cablivi, should be closely monitored for platelet counts and signs of aTTP for early diagnosis of relapse after stopping or interrupting use of Cablivi."[1] While the clinical trial had a clear maximum duration of treatment (58 days post–daily PEX cessation) and the product monograph specifies treatment may be extended by a maximum of 28 days and should be discontinued if the patient experiences more than two recurrences of aTTP while on caplacizumab, it is not clear how long treatment will continue for patients with persistent recurrence risk factors in real-world clinical practice. As only one recurrence of aTTP was possible within the model, the economic impact of either multiple recurrences or discontinuing caplacizumab therapy following two recurrences could not be considered.

Patient Input

Input was received from the Answering TTP Foundation with the assistance of the Canadian Organization for Rare Disorders. The two patient groups developed a survey and conducted interviews and received feedback from 257 respondents, 83% of whom were patients with TTP, and 17% of whom were living in Canada. Patients described living with aTTP as unlike most chronic diseases in that the difficulty was not in day-to-day experience, but in acute aTTP episodes. While 21% of respondents had not had a relapse since their diagnosis, 49% had experienced one or two relapses, while the remainder had experienced three to more than 10.

Patient responses highlighted the severity of an acute episode, including those that resulted in the patient dying. The responses described a significant impact on quality of life as a result of an aTTP episode. Patients reported a financial burden due to an impact on their ability to work, lost income due to missed work, and the cost of paying for treatment. This, in addition to stress and mood swings, which were reported as side effects, had an impact on friends and family. Respondents also described feelings of anxiety, worry, and fear about the onset of a future episode.

Most respondents regarded PEX as effective, and those who did not often referred to PEX not being administered soon enough or without a backup strategy. Almost all patients had received corticosteroids, and many had received rituximab, although it is unclear what proportion of Canadian patients had received rituximab. Although few responding patients had experience with caplacizumab, those who did expressed positive opinions, especially those who had previous aTTP episodes for comparison. (See Stakeholder Engagement: Patient Input in the CADTH CDR Clinical Report and the CDR patient group input submission report for caplacizumab.)

Conclusions

In adult patients with aTTP, the use of caplacizumab in addition to SOC reduced the frequency of aTTP recurrence within the active treatment and follow-up periods of the HERCULES trial and was associated with one patient death within the same time period, compared with three deaths in patients treated with SOC alone. This possible difference in mortality is a key driver in the economic model.

CADTH's base-case reanalysis concluded that, at the submitted price, the addition of caplacizumab to SOC was associated with an ICER of $237,053 per QALY compared with SOC alone. At a WTP of $50,000 per QALY, the price of caplacizumab would need to be reduced by approximately 75% to be considered cost-effective.

CADTH was unable to consider future aTTP episodes, specifically, the potential impact of caplacizumab treatment on reducing or delaying them, or the costs associated with further treatment for acute episodes. Additionally, the vast majority of incremental QALYs gained within the model occurred during the extrapolated remission period rather than during the acute phase for which data exists. As such, assumptions around the quantity and quality of life experienced by patients who survive an aTTP episode are key drivers of the cost-effectiveness results. With little data available regarding these outcomes, the resulting ICER is uncertain.

Appendix 1: Cost Comparison

The comparators presented in Table 5 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs but may be devices or procedures. Costs are sponsor's list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 5: CDR Cost Comparison of Prescribed Drug Indicated for Adults With aTTP

Drug or comparator	Strength	Dosage form	Price ($)	Recommended dose	Average daily drug cost ($)	Drug cost for duration of treatment ($)
Caplacizumab (Cablivi)	11 mg	11 mg powder for solution	6,200.00[a]	11 mg	• Day 1 of treatment: 12,400 • Subsequent days of treatment: 6,200	• Average duration of therapy:[b] [redacted] • Maximum duration of therapy:[c] [redacted]

aTTP = acquired thrombotic thrombocytopenic purpura; CDR = CADTH Common Drug Review; PEX = plasma exchange.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed October 2019) unless otherwise indicated and do not include dispensing fees. Does not include use of open-label caplacizumab, which was used in the event of aTTP recurrence requiring re-initiation of daily PEX.

[a] Sponsor-submitted price.

[b] Based on an average duration of caplacizumab treatment of [redacted] days for an acute aTTP episode, as outlined in the HERCULES trial.[6]

[c] Maximum therapy duration included an average duration of [redacted] days of PEX and the maximum 28 possible days of additional therapy after cessation of PEX.

Table 6: CDR Cost Comparison of Standard-of-Care Therapies for Adults With aTTP

Drug or comparator	Strength	Dosage form	Price ($)	Recommended dose	Average daily drug cost ($)	Drug cost for duration of treatment ($)[a]
Plasma exchange	250 mL unit	Blood product for infusion	122.01[b]	1.5 plasma volume (60 mL/kg)	• 70 kg patient: 2,047.77 • 85 kg patient: 2,489.00	• 70 kg patient: 12,299 • 85 kg patient: 14,934
Adjunctive therapies						
Prednisone (generic, Winpred 1 mg tablet)	50 mg 5 mg 1 mg	Tablet	0.1735 0.0220 0.1066	1 mg/kg until taper[c]	0.26	3
Methylprednisolone (Medrol)	100 mg/5 mL solution	Injectable	13.4259	1,000 mg	134.26	403
Rituximab (off-label)	10 mg/mL solution	Injectable	48.2305[d]	375 mg/m^2/week[c]	465.08	13,022

aTTP = acquired thrombotic thrombocytopenic purpura; CDR = CADTH Common Drug Review.

Note: All prices are from the Ontario Drug Benefit Formulary[12] (accessed October 2019) unless otherwise indicated and do not include dispensing fees.

[a] Based on average duration of therapy during an acute aTTP event without exacerbation as reported in the sponsor's submission.

[b] Price as reported by sponsor of caplacizumab; CADTH was unable to independently confirm.

[c] Average patient weight of 70 kg and average body surface area of 1.8 m^2 were used for the calculation of average drug costs per day and for the duration of treatment.[24]

[d] Saskatchewan Formulary (October 2019).[25]

Appendix 2: Summary of Key Outcomes

Table 7: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is Caplacizumab Plus SOC Relative to SOC Alone?

Caplacizumab plus SOC versus SOC	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	N/A
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	Sponsor's base-case analysis: $72,786 per QALY CADTH base-case analysis: $237,053 per QALY					

CE = cost-effectiveness; N/A = not applicable; QALY = quality-adjusted life-year; SOC = standard of care.

Appendix 3: Additional Information

Table 8: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments Reviewer to provide comments if checking "no"	Scenario and sensitivity analyses methods and assumptions were unclearly reported		
Was the material included (content) sufficient?	X		
Comments Reviewer to provide comments if checking "poor"	None		
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking "poor"	Inputs within model and associated report were unusually organized, making them difficult to locate and understand		

Table 9: Authors Information

Authors of the pharmacoeconomic evaluation submitted to CDR

☐ Adaptation of Global model/Canadian model done by the sponsor

☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the sponsor

☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the sponsor

☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document			X
Authors had independent control over the methods and right to publish analysis			X

CDR = CADTH Common Drug Review.

Appendix 4: Summary of Other HTA Reviews of Drug

No other health technology assessment agencies had completed an economic review of caplacizumab (Cablivi) for the requested CADTH CDR indication at the time of this report.

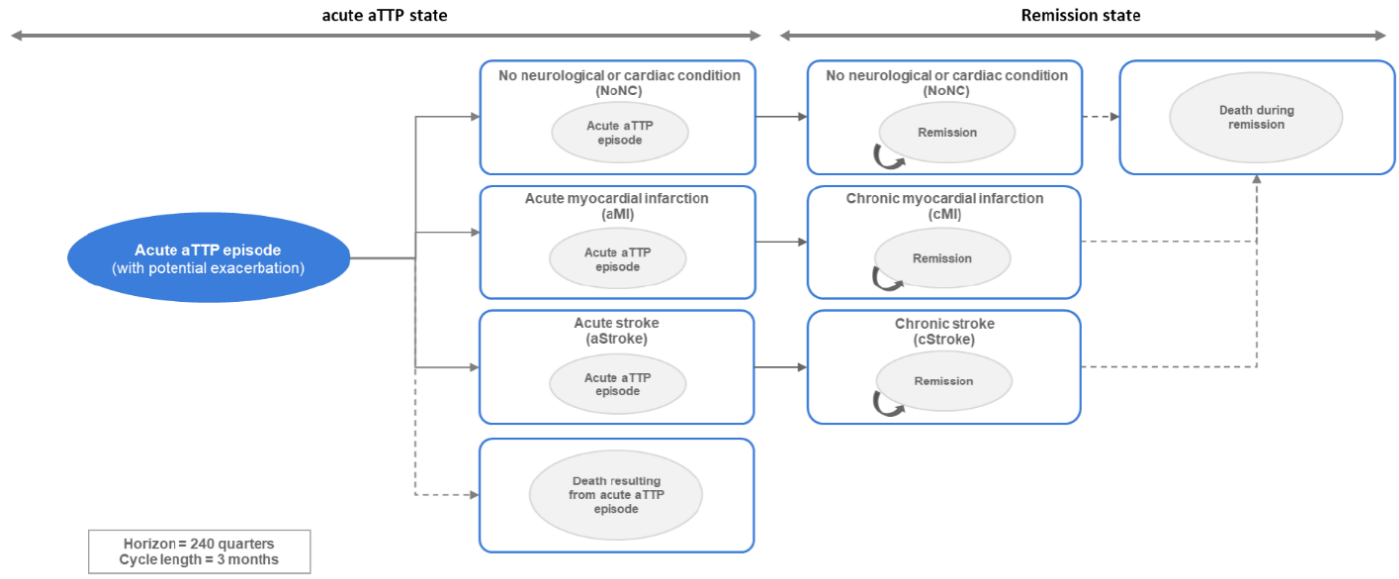
Caplacizumab (Cablivi) is currently under review by the National Institute for Health and Care Excellence (NICE, UK)[26] and the Institut national d'excellence en santé et en services sociaux (INESSS, Quebec).[27] The Haute Autorité de Santé (HAS, France)[28] has decided that due to the lack of significant impact of caplacizumab on health insurance expenses, it will not conduct a health economic study. Similarly, the Institute for Quality and Efficiency in Health Care (IQWiG, Germany)[29] reviewed caplacizumab for adults suffering from an acute aTTP episode. No English summary was available; however, it was determined that the benefit of caplacizumab, as an orphan drug, was considered as proven by its authorization and is therefore reimbursed.

Appendix 5: Reviewer Worksheets

Sponsor's Model Structure

As outlined in Figure 1, the model followed a cohort of patients who had suffered an index acute aTTP episode. In the first cycle, patients entered one of four different acute disease health states: acute MI, acute stroke, no neurological or cardiac condition, or death. After the first cycle, patients who died transitioned into the "death resulting from acute aTTP health state," while patients who remained alive transitioned into one of the remission health states. If the patient had not suffered an MI or stroke during the first cycle, they would transition into the "no neurologic or cardiac condition" remission health state. Patients who experienced an acute MI or an acute stroke would transition into the "chronic MI" or "chronic stroke" remission health states, respectively. Patients remained in their respective remission health states until death.

Figure 1: Sponsor's Model Structure



aMI = acute myocardial infarction; aStroke = acute stroke; aTTP = acquired thrombotic thrombocytopenic purpura; cMI = chronic myocardial infarction; NoNC = no neurological or cardiac condition.

Source: Sponsor's Pharmacoeconomic Report, Figure 7-1.[15]

Table 10: Data Sources

Data input	Description of data source	Comment
Baseline characteristics	Mean age, sex proportion, mean platelet count level, previous TTP episodes, and ADAMTS13 activity was obtained from the HERCULES trial.[6]	Appropriate.
Efficacy	Probabilities of experiencing an exacerbation (defined as a reduction in platelet count below 150 × 10^9/L, an increased LDH level, and the need to restart PEX therapy, all of which must occur less than 30 days after the last PEX with clinical response), MI, stroke, or death during the index aTTP event were derived from the HERCULES trial for patients receiving caplacizumab and SOC therapy.[6]	Source was appropriate. However, by selecting estimates from different sources for caplacizumab with SOC and SOC alone without proper adjustment to account for relative treatment effects, the approach taken to combine treatment estimates was inappropriate. See Limitations of the Sponsor's Submission within the CADTH CDR Clinical Review Report. The model did not include aTTP relapses from the HERCULES trial, all of which occurred in the caplacizumab treatment group within several days of treatment discontinuation. An aTTP relapse was defined as a reduction in platelet count below 150 × 10^9/L, an increased LDH level and the need to restart PEX therapy all occurring more than 30 days after the last PEX and a clinical response to PEX. See Limitations of the Sponsor's Submission within the CADTH CDR Clinical Review Report. Imbalances existed in the HERCULES trial at baseline, with patients in the caplacizumab plus SOC group having had fewer previous TTP episodes and a higher proportion of patients with ADAMTS13 activity ≥ 10%, but also a higher proportion assessed as having severe disease. It is unclear what impact these imbalances may have had on relative treatment effect. See CADTH CDR Clinical Report for caplacizumab, Table 4.
Natural history	The sponsor conducted a systematic literature review. The probabilities of developing concurrent MI or stroke within an aTTP episode were derived from Goel et al. (2016).[7] The probability of experiencing an exacerbation from an aTTP event was sourced from a meta-analysis conducted by the sponsor.[5]	Acceptable. Goel et al. investigated aTTP and associated events in a US population but did not break down the MI or stroke data by age.[7] This study included patients < 18 years of age, which was outside the current clinical indication for caplacizumab (i.e., for adult patients suffering from an acute aTTP episode in combination with PEX and immunosuppressive therapy). However, patients less than 18 years old accounted for approximately 1.3% of the study population and likely had a small effect on disease progression.[7] Acquired TTP is associated with long-term neurocognitive impairments[30] that were not included in the sponsor's model. Psychological effects, memory loss, and/or confusion were listed as chronic issues for many patients, as outlined in the patient input submitted for this review. Caplacizumab's neurocognitive impact on the treated aTTP population was not investigated in the HERCULES trial.[6] Although neurocognitive impairment may impact the quality of life of patients post–aTTP episode, there is insufficient evidence to suggest a difference between patients treated with caplacizumab plus SOC compared with SOC alone.

Data input	Description of data source	Comment
Utilities	Gender- and age-specific utilities were approximated from UK values published in 1999.[8]	Less generalizable. More recent data on health utilities in the general Canadian population are available.[19]
	Disutility of an acute aTTP episode was approximated using EQ-5D results from Anie et al. in 2012, which studied sickle cell disease.[16]	No published data exists on the disutility associated with an acute aTTP episode. Although clinical experts consulted by CADTH noted that sickle cell disease significantly differs in disease management and hospitalization, they concluded sickle cell disease was an appropriate proxy for an acute aTTP episode due to the lack of a more appropriate proxy.
	Utility multiplier for acute MI and acute stroke were based on NICE clinical guideline 181.[9] Disutility of thromboembolic events, such as deep vein thrombosis and pulmonary embolism, were based on NICE TA 327.[31] Other AEs, such as treatment-related serious bleeding events, were based on NICE TA 327 and TA 420 guidance.[31,32]	Utility multipliers and disutilities associated with acute conditions and adverse treatment events were validated by CADTH. The validity of applying constant utility multipliers over a lifetime is uncertain; however, these inputs were minor drivers in the sponsor's model and did not significantly impact the resulting incremental cost-utility ratio.
	The sponsor assumed the disutility of PEX complications would be similar to the disutility of a bleeding event, as seen in NICE TA 327 guidance.[31]	Likely not acceptable, but unlikely to impact the model. Clinical experts consulted by CADTH noted that, in practice, the major adverse effect with PEX therapy is an allergic reaction; therefore, equating PEX adverse effects to serious bleeding did not appropriately capture the expected utility impact.
AEs	The probabilities of thromboembolic and other AEs, such as PEX complications and treatment-related serious bleeding events, were based on data from the HERCULES trial.[6]	The sponsor's calculation of PEX complications, using the proportion of mild versus major adverse events, was not transparent in the model. However, this is unlikely to impact the model.
Mortality	The probability of death from an acute aTTP episode for patients who underwent standard therapy was derived by a systematic literature review by the sponsor. Mortality data for an acute aTTP event in patients who received adjunctive therapy with caplacizumab was derived from the HERCULES trial.[6]	Inappropriate. See Limitations of the Sponsor's Submission within the main body of this report.
	Mortality ratios for patients who suffered a stroke was derived from Rutten-Jacobs et al.[33] Mortality ratios for patients who suffered from MI was derived from a study performed by SOLVD investigators published in 1992.[34]	Mortality ratios for both MI and stroke did not change, regardless of length of time from event (acute and chronic values were equal).[34,33] The mortality ratio for MI was based on a comparison between patients with and without congestive heart failure, not MI or coronary artery disease.[34] However, these inputs did not significantly impact the cost utility of caplacizumab.
Resource use and costs		
Drug	Sponsor-submitted price for caplacizumab. The pivotal trial publication[3] defined the dose of caplacizumab as 10 mg per vial, whereas the FDA[35] and Health Canada[1] have defined identical vials as 11 mg per dose.	Appropriate. The product is unchanged from that used in the trial.
	The sponsor estimated the costs of PEX by doing internal market research and using internal data on plasma usage from the Canadian Apheresis Group.	Uncertain. CADTH was unable to validate these values independently. CADTH conducted a scenario analysis on the cost of PEX.

Data input	Description of data source	Comment
	The cost of corticosteroids (prednisolone and prednisone) and rituximab were sourced from the Ontario Drug Benefit Formulary and the Ontario Drug Benefit Exceptional Access Program.[12,17]	Acceptable source.
Administration	The procedural cost of PEX administration and the additional outpatient cost of rituximab therapy were sourced from the Ontario Ministry of Health and Long-Term Care Schedule of Benefits – Physician Services.[12] No costs regarding administration by a health care worker or self-administration were included for caplacizumab.	Acceptable. As cited in the draft product monograph, the first dose of caplacizumab would be administered by a health care worker in hospital and subsequent doses would be self-administered by the patient. No additional administration cost was assumed for the first dose of caplacizumab and the additional costs of subsequent doses were assumed to be included within the cost of a hematology specialist outpatient visit.
AEs	No costs associated with the management of AEs with the exception of severe treatment-related bleeding or thromboembolic events were included.[6]	Pulmonary embolism, deep vein thrombosis, PEX complications, and other bleeding were assumed to incur no additional cost, as the sponsor concluded that the resources which would be used to manage these events would have already been included as part of the inpatient stay.
Health state	Components of each health state were sourced from: • the Ontario Ministry of Health and Long-Term Care[12] • the Canadian Institute for Health Information[10] • physician feedback (for ADAMTS13 assay) • internal market research • the Ontario Drug Benefit Formulary[12] • the Ontario Drug Benefit Formulary Exceptional Access Program[17]	Acceptable. The sponsor assumed that the additional costs of chronic MI and chronic stroke health states were limited to consults and diagnostic/monitoring tests only.

ADAMTS13 = and metalloproteinase with a thrombospondin type 1 motif, member 13; AE = adverse event; aTTP = acquired thrombotic thrombocytopenic purpura; EQ-5D = EuroQol 5-Dimensions; LDH = lactate dehydrogenase; MI = myocardial infarction; NICE = National Institute for Health and Care Excellence; PEX = plasma exchange; SOC = standard of care; TA = technology appraisal.

Table 11: Sponsor's Key Assumptions

Assumption	Comment
The mortality for patients in the caplacizumab group who had an acute aTTP event without acute stroke or MI was equivalent to the mortality of the general population (relative risk of 1.0 when compared with standard of care).	Inappropriate. See Limitations of the Sponsor's Submission within the main body of this report.
Model inputs pertaining to inpatient stay (i.e., length of hospital stay, disutility, and treatment) for a recurrence of aTTP were the same as those for patients who did not have a subsequent episode.	Acceptable. No current data exists comparing the length of hospitalization and disutility of an acute aTTP episode to exacerbation. Clinical experts consulted by CADTH noted that the major difference in management for recurrent disease compared with the initial acute episode was the increased use of adjunctive immunosuppressive therapies. These clinical experts stated that in recurrent admission, more than 25% of patients who were admitted to hospital would receive rituximab, which supports the sponsor's model assumption.
Subsequent acute aTTP events were not modelled.	Inappropriate. See Limitations of the Sponsor's Submission within the main body of this report.
Costs and utilities associated with intracerebral hemorrhage, TTP, and thrombotic microangiopathy were not included, as they were included elsewhere (i.e., intracerebral hemorrhage was considered under stroke).	Acceptable. Although this assumption did not fully encapsulate the disutility and costs experienced by aTTP patients suffering from these illnesses, model simulations were run incorporating greater treatment-related disutility and health state–related costs. These simulations demonstrated that large variation in disutility and costs related to adverse events did not significantly impact the cost utility of caplacizumab.
Patients experiencing the index acute aTTP episode were treated in the hospital.	Appropriate.
Prior to the index acute aTTP episode, patients were free of chronic or comorbid conditions and therefore had identical mortality to the general population.	Inappropriate. See Limitations of the Sponsor's Submission within the main body of this report.
The duration of an acute aTTP episode in hospital was assumed to be equivalent to the number of days the patient spent in hospital during an aTTP exacerbation.	Appropriate.

aTTP = acquired thrombotic thrombocytopenic purpura; CDR = CADTH Common Drug Review; MI = myocardial infarction; TTP = thrombotic thrombocytopenic purpura.

Table 12: Sponsor's Disutilities and Utility Modifiers

Event	Disutility or multiplier	SOC		Caplacizumab + SOC	
		Duration	Frequency or rate	Duration	Frequency or rate
Disutility					
Acute aTTP episode, initial	−0.230	10.8 days (length of hospital stay)	All	9.5 days (length of hospital stay)	All
Acute aTTP episode, recurrence (%)	−0.230	10.9 days (length of hospital stay)	[redacted]%	9.5 days (length of hospital stay)	[redacted]%
Pulmonary embolism (%)	−0.250	6 weeks	0%	6 weeks	1.41%
Deep vein thrombosis (%)	−0.250	6 weeks	4.11%	6 weeks	4.2 (3%)

Event	Disutility or multiplier	SOC		Caplacizumab + SOC	
		Duration	Frequency or rate	Duration	Frequency or rate
PEX complication (rate per patient)	−0.050	4.4 days	1.29	4.4 days	0.57
Treatment-related serious bleeding (rate per patient)	−0.100	10.8 days	0	10.8 days	0.13
Utility multiplier					
Non-fatal MI (acute)	0.400	One 90-day cycle	4.39%	One 90-day cycle	4.52%
Non-fatal stroke (acute)	0.628	Four 90-day cycles	4.44%	Four 90-day cycles	3.06%
Non-fatal MI (subsequent cycles)	0.880	Remainder of lifetime	Risk of mortality multiplier: 2.02	Remainder of lifetime	Risk of mortality multiplier: 2.02
Non-fatal stroke (subsequent cycles)	0.628	Remainder of lifetime	Risk of mortality multiplier: 3.90	Remainder of lifetime	Risk of mortality multiplier: 3.90

aTTP: acquired thrombotic thrombocytopenic purpura; MI = myocardial infarction; PEX = plasma exchange; SOC = standard of care.

Source: Adapted from sponsor's submitted pharmacoeconomic evaluation, tables 8-18, 8-19, 8-23, 8-24, 8-25, 8-26, 8-29, and 8-31.[15]

Sponsor's Results

Overall results for the sponsor's base case can be found in Table 2. Costs broken down by category are presented in Table 12 and are mainly driven by the cost of caplacizumab, with some savings seen in the cost of acute treatment (i.e., mainly PEX) and hospitalization due to decreased time in the ICU.

Table 13: Sponsor's Base Case Cost Results by Category

Costs per patient	SOC ($)	Caplacizumab + SOC ($)	Incremental costs (savings, $)
Acute aTTP episode cost			
Acute treatment (excluding caplacizumab)	23,050	16,062	(6,988)
Caplacizumab	0	239,691	239,691
Adverse event	0	0	0
Hospitalization	25,472	14,639	(10,833)
Monitoring	2,674	2,075	(600)
Remission cost			
Chronic disease (post-MI or post-stroke)	2,641	2,354	(287)
Monitoring	13,881	16,075	2,194
Death	0	0	0
Total cost per patient	**67,546**	**290,955**	**223,408**

aTTP = acquired thrombotic thrombocytopenic purpura; MI = myocardial infarction; SOC = standard of care.

The majority of QALY gain for the caplacizumab plus SOC group is due to the increased probability of mortality modelled in the SOC group, leading to greater QALYs accumulating in the extrapolated remission phase of the model (Table 14).

Table 14: Sponsor's Base Case Discounted QALY Results by Health State

	SOC (QALYs)	Caplacizumab + SOC (QALYs)	Incremental QALYs (negative)
Acute aTTP episode cycle (90 days)			
No neurological or cardiac condition	0.189	0.193	0.005
Acute stroke	0.005	0.003	(0.002)
Acute MI	0.003	0.003	0.000
Remission cycles (remainder of lifetime)			
No neurological or cardiac condition	17.586	20.762	3.176
Chronic stroke (post-stroke)	0.409	0.281	(0.128)
Chronic MI (post-MI)	0.657	0.676	0.018
TOTAL	**18.849**	**21.919**	**3.069**

aTTP = acquired thrombotic thrombocytopenic purpura; MI = myocardial infarction; QALY = quality-adjusted life-year; SOC = standard of care.

A summary of the sponsor's deterministic results for the incremental cost per life-year gained can be found in Table 15.

Table 15: Summary of the Sponsor's Deterministic Results for Life-Years

	Total costs ($)	Incremental cost of caplacizumab ($)	Total life-years	Incremental life-years for caplacizumab	Incremental cost per life-year ($ per life-year gained)
SOC	67,996	Reference	24.265	Reference	Reference
Caplacizumab + SOC	290,737	222,740	28.070	3.80	58,545

SOC = standard of care.

CADTH CDR Reanalyses

CADTH's base-case analysis is outlined in Table 3. Cost and QALY breakdowns of the CADTH base-case results can be found in Table 16 and Table 17, respectively.

Differences in the CADTH reanalysis results compared with the sponsor's analysis are driven by the inclusion of mortality in the caplacizumab group during the acute phase, as well as increased mortality and lowered utility weights for both groups in the remission phase.

Table 16: CADTH Base Case Cost Results by Category

Costs per patient	SOC ($)	Caplacizumab + SOC ($)	Incremental costs (savings, $)
Acute aTTP episode cost			
Acute treatment (excluding caplacizumab)	23,364	17,799	(5,565)
Caplacizumab	0	260,350	260,350
Adverse event	0	0	0
Hospitalization	25,855	15,834	(10,022)
Monitoring	2,714	2,185	(529)
Remission cost			
Chronic treatment	2,557	3,970	1,413

Costs per patient	SOC ($)	Caplacizumab + SOC ($)	Incremental costs (savings, $)
Monitoring	11,225	12,128	903
Death	0	0	0
Total cost per patient	**65,697**	**312,264**	**246,568**

aTTP = acquired thrombotic thrombocytopenic purpura; SOC = standard of care.

Table 17: CADTH Base Case Discounted QALY Results by Health State

	SOC (QALYs)	Caplacizumab + SOC (QALYs)	Incremental QALYs (negative)
Acute aTTP episode cycle (90 days)			
No neurological or cardiac condition	0.175	0.181	0.006
Acute stroke	0.005	0.004	0.000
Acute MI	0.003	0.004	0.001
Remission cycles (remainder of lifetime)			
No neurological or cardiac condition	13.385	14.350	0.965
Chronic stroke (post-stroke)	0.405	0.385	(0.019)
Chronic MI (post-MI)	0.565	0.652	0.088
TOTAL	**14.536**	**15.576**	**1.040**

aTTP = acquired thrombotic thrombocytopenic purpura; MI = myocardial infarction; QALY = quality-adjusted life-year; SOC = standard of care.

Note: Some totals may appear off due to rounding.

Scenario analyses exploring uncertainty in the CADTH base case can be found in Table 18. Scenario A, the societal perspective (as programmed by the sponsor), did not impact the ICER, as productivity savings during the acute phase of the model appear to be offset by increased productivity loss due to future monitoring and chronic treatment costs due to more patients surviving. Scenario B, where the probability of death for the SOC arm was based on that observed in the HERCULES trial, results in a much higher ICER, as a reduction in the absolute risk of death during the acute aTTP phase in the SOC group (from [redacted]% to 4.1%) leads to fewer patients benefiting when the RR is applied for the caplacizumab plus SOC group. Scenario C, where the quality of life associated with living with aTTP is assumed to be equivalent to having a mood disorder rather than equivalent to asthma, leads to a moderate increase in the ICER, as the lower utility weight applied (multiplier of 0.75 versus 0.93 in the base case) reduces the overall accumulation of QALYs for all surviving patients. Finally, as the per-unit cost of PEX therapy could not be confirmed by CADTH, sensitivity analyses assuming the unit cost was halved and doubled are presented in scenario D and E, respectively. As caplacizumab use leads to a small reduction in PEX therapy duration, the ICER for caplacizumab plus SOC compared with SOC alone is slightly lower when PEX is more expensive and slightly higher when PEX is less expensive than the cost of PEX assumed in the sponsor's and CADTH's base cases.

Table 18: CADTH Scenario and Sensitivity Analyses Around the Base Case

	Description	CADTH base-case value	Scenario value	Incremental cost ($)	Incremental QALYs	ICER ($/QALY)
	CDR base case	**Reference**		**246,568**	**1.04**	**237,053**
A	Societal perspective	Public health care payer perspective, no productivity loss included	Includes sponsor's estimates of productivity loss and average wage	246,260	1.03	238,158
B	Probability of death in first cycle direct from HERCULES trial	• Caplacizumab + SOC = [redacted]% • SOC = [redacted]% • Mean RR = 0.34	• Caplacizumab + SOC = 1.4% • SOC = 4.1% • Mean RR = 0.34	245,853	0.21	1,195,347
C	Mood disorder utility as proxy for aTTP in remission	• Multiplier consistent with asthma utility score: 0.93	• Multiplier consistent with mood disorder utility score: 0.75	246,421	0.82	300,064
D	PEX unit cost halved	$122.01 per unit	$61.00 per unit	249,022	1.03	242,878
E	PEX unit cost doubled	$122.01 per unit	$244.02 per unit	241,136	1.05	229,423

aTTP = acquired thrombotic thrombocytopenic purpura; CDR = CADTH Common Drug Review; ICER = incremental cost-effectiveness ratio; PEX = plasma exchange therapy; QALY = quality-adjusted life-year; RR = relative risk; SOC = standard of care.

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