CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(FINAL)

CAPLACIZUMAB (CABLIVI — Sanofi-Aventis Canada Inc.)
Indication: For the treatment of adults with acquired thrombotic thrombocytopenic purpura.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that caplacizumab not be reimbursed for the treatment of adults with acquired thrombotic thrombocytopenic purpura.

Service Line:	CADTH Drug Reimbursement Recommendation
Version:	FINAL
Publication Date:	September 1, 2020
Report Length:	8 Pages

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Indication: For the treatment of adults with acquired thrombotic thrombocytopenic purpura.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that caplacizumab not be reimbursed for the treatment of adults with aTTP.

Reasons for the Recommendation

1. Although one phase III, double-blind, randomized controlled trial (RCT) (HERCULES, N = 145) in adults with acquired thrombotic thrombocytopenic purpura (aTTP) receiving plasma exchange (PEX) and immunosuppression demonstrated that caplacizumab statistically significantly reduced the time to normalization of platelet count, the 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. Limitations in the design of the reviewed studies precluded CDEC from determining whether caplacizumab provides clinically meaningful value compared with PEX plus immunosuppression alone.
2. HERCULES and a supportive phase II RCT (TITAN, N = 75) provided data on the effects of caplacizumab versus placebo for up to two aTTP episodes only. As such, CDEC could not determine caplacizumab's benefit, if any, beyond the duration of the trials.
3. The variability in the natural history of aTTP and the limitations in the design and analysis of HERCULES prevented CDEC from identifying a subpopulation of patients with aTTP that is most likely to benefit from treatment with caplacizumab.

Discussion Points

- 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.
- CDEC discussed that in the overall study period of the HERCULES trial, treatment with caplacizumab was associated with a numeric reduction in the total PEX volume and a shorter duration of PEX therapy compared with placebo. However, given that no prespecified statistical comparisons were conducted in the analysis of these data, imbalances existed in the baseline characteristics of the two groups, and there was a lack of long-term clinical outcome data, CDEC found it difficult to interpret these findings.
- An important outcome identified by patients is a reduction in the risk and rate of experiencing relapses of aTTP. Unfortunately, the design and duration of HERCULES were insufficient to assess the effects of caplacizumab on the rate of relapse beyond the trial's duration.
- According to clinical experts consulted by CADTH, the percentage of patients who received rituximab in the HERCULES study was higher than what is expected in Canada. Given that 40% of patients in the overall HERCULES trial period received caplacizumab in addition to rituximab (and PEX plus corticosteroids), it is unclear if the observed effects of caplacizumab in the trial would be observed in Canadian practice.

Background

Caplacizumab is a humanized, bivalent nanobody targeting the A1 domain of von Willebrand factor to inhibit the interaction between von Willebrand factor and platelets. The Health Canada–approved indication is for the treatment of adults with aTTP in combination with plasma exchange and immunosuppressive therapy. Caplacizumab is available as powder for solution (11 mg per vial) for IV or subcutaneous (SC) injection. The recommended dosage of caplacizumab, to be administered upon initiation of PEX, is according to the following schedule:

- First day of treatment: An 11 mg bolus IV injection at least 15 minutes prior to PEX, followed by an 11 mg SC injection after completion of PEX on that day.

- Subsequent days of treatment during PEX: A daily 11 mg SC injection following PEX.
- Treatment after PEX period: Injections of 11 mg SC once daily for 30 days following the last daily PEX. If, after the initial treatment course, sign(s) of persistent underlying disease, such as suppressed disintegrin-like and metalloproteinase with thrombospondin repeats 13 activity levels, remain present, treatment may be extended for a maximum of 28 days.

According to the product monograph, caplacizumab should be discontinued if the patient experiences more than two recurrences of aTTP while on caplacizumab. Cases of relapse have been reported shortly after discontinuation of caplacizumab treatment, especially in cases of unresolved underlying autoimmune disease.

Submission History

Caplacizumab was not previously reviewed by the CADTH Common Drug Review for the treatment of aTTP.

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CADTH: a systematic review of one randomized controlled trial of caplacizumab, a review of supportive data from a phase II RCT, and a critique of the sponsor's pharmacoeconomic evaluation. The committee also considered input from clinical experts with experience in treating patients with aTTP, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

One patient group, the Answering TTP Foundation (with the support of the Canadian Organization for Rare Disorders), provided input for this submission. Patient perspectives were obtained from a survey and interviews with patients, caregivers or family members, and health care professionals in Canada, as well as in other countries. The following is a summary of key input from the perspective of the patient group:

- The Answering TTP Foundation indicated that challenges of aTTP are mostly the result of acute TTP episodes, which can be life-threatening and require intensive treatment. Patients' quality of life was significantly impacted as a result of an aTTP episode. Canadian patients expressed a sense of frustration with challenges to obtaining an initial diagnosis and receiving timely care for the acute episodes. In addition, patients highlighted the financial burden associated with the disease and treatment.
- Almost all respondents reported experience with PEX and corticosteroids, and 70% of them had or were currently receiving rituximab. Timely access to PEX was a challenge for some patients. When PEX was unable to stabilize platelet counts, patients reported limited options for effective treatment. In addition, patients reported experiencing adverse events with PEX, which were sometimes serious in nature. Patients also noted adverse events associated with receiving corticosteroids and other treatments for aTTP.
- Approximately 5% to 6% of respondents had received caplacizumab. The feedback regarding treatment with caplacizumab was positive, particularly regarding time to response (platelet control recovery), time spent in hospital, and improved physical and mental well-being. Patients also reported experiencing minimal side effects associated with the use of caplacizumab (primarily minor, localized bleeding in soft tissues such as the gums).
- Patients expressed a desire for a new treatment to provide faster normalization of platelet counts, reduced frequency and length of PEX, shorter hospital stays, quicker return to normal life, improved survival, and reduced disease relapse.

Clinical Trials

The systematic review included one phase III, double-blind RCT (HERCULES, N = 145) that evaluated the efficacy and safety of caplacizumab in adult patients with aTTP. Eligible participants were randomized to receive caplacizumab 11 mg or placebo, in addition to standard of care, which consisted of PEX and corticosteroid treatment, as well as other immunosuppressive drugs, per study site treatment procedures for aTTP. The double-blind treatment phase consisted of a daily PEX period plus a 30-day post-daily PEX period. A treatment extension phase of seven to 28 days with the patient's originally assigned treatment (caplacizumab or placebo) was allowed for those with risk factors of relapse of the presenting aTTP episode. During the double-blind treatment period of HERCULES, in cases of first exacerbation or relapse of the presenting aTTP episode, patients would receive open-label

caplacizumab together with daily PEX irrespective of what the initial treatment allocation was. After treatment, all patients were followed for four weeks. The primary efficacy outcome of this study was time to platelet count response (defined as initial platelet count ≥ 150 × 10^9/L with subsequent stop of daily PEX within five days of treatment). Other efficacy outcomes included prevention of recurrence of aTTP, prevention of refractory aTTP, prevention of major thromboembolic event, normalization of organ damage markers, and intensive care unit (ICU) or hospital stay related to aTTP episodes. A composite end point including aTTP-related death, recurrence of aTTP, or a thromboembolic event during the treatment period were assessed as well. Health-related quality of life was not assessed. The median duration of exposure to caplacizumab during the double-blind period was 35 days (maximum of 65 days).

Key limitations of HERCULES included potential biases on the study results due to imbalanced patient baseline characteristics, uncertainty around the validity of using platelet count for treatment effect evaluation, missing data for some efficacy outcomes, and a lack of statistical testing and/or adjustments for multiplicity for some of the clinically relevant secondary efficacy outcomes. Long-term clinical benefits and harms were not explored in HERCULES due to its duration.

Outcomes

Outcomes of interest were defined a priori in CADTH's systematic review protocol. Of these, the committee discussed survival, reduction in use of PEX, aTTP recurrence, organ damage, prevention of major thromboembolic events, prevention of refractory aTTP to treatment, platelet count response, and hospitalization due to aTTP episodes. The absence of health-related quality of life data was noted.

Efficacy

Survival

One patient from the caplacizumab group died during the drug-free follow-up period; the death was not considered by the study investigators to be related to caplacizumab. Three patients from the placebo group died during the daily PEX period.

Reduction in Use of PEX

During the overall study period, treatment with caplacizumab was associated with a shorter duration of PEX therapy compared with placebo (mean days on PEX = 5.8 [standard error (SE) = 0.5] for caplacizumab and 9.4 [SE = 0.8] for placebo). Treatment with caplacizumab was also associated with reduced total PEX volume compared with placebo (21.3 [SE = 1.6] litres versus 35.9 [SE = 4.2] litres, respectively). According to the clinical experts consulted for this review, the between-group differences in the number of days on PEX and the PEX volume were considered clinically relevant. However, no statistical comparisons were conducted in the analysis of these data, making it difficult to interpret the findings.

aTTP Recurrence

During the overall study period, a statistically significantly (P = 0.0004) lower percentage of patients in the caplacizumab group (nine patients; 12.7%) compared to the placebo group (28 patients; 38.4%) experienced recurrence of aTTP, either as an exacerbation or a relapse. Exacerbations occurred in three patients (4.2%) treated with caplacizumab and 28 patients (38.4%) treated with placebo during the double-blind treatment period. Relapses occurred in six patients (9.1%) treated with caplacizumab but no patients in the placebo group during the follow-up period.

Organ Damage

The median time to normalization of all three organ damage markers (lactate dehydrogenase, cardiac troponin, and serum creatinine) was 2.86 days (95% confidence interval [CI], 1.93 to 3.86) in the caplacizumab group and 3.36 days (95% CI, 1.88 to 7.71) in the placebo group, respectively. [redacted]

Prevention of Major Thromboembolic Events

During the overall treatment period, the number of patients experiencing major thromboembolic events was similar between the caplacizumab group 6 (8.5%) and the placebo group 6 (8.2%).

Prevention of Refractory aTTP to Treatment
During the double-blind treatment period, no patients in the caplacizumab group and three patients (4.2%) in the placebo group were considered to have refractory aTTP. The between-group difference in refractory aTTP was not statistically significant.

Platelet Count Response
A statistically significantly shorter time to normalization of platelet count was observed in the caplacizumab group compared to the placebo group (rate ratio for normalization of platelet count [95% CI]: 1.55 [1.09 to 2.19]; P=0.01), with a median time to normalization of 2.69 days in the caplacizumab group versus 2.88 days in the placebo group.

Hospitalization Due to aTTP Episodes

Mean (SE) number of days in the ICU during the daily PEX period was [redacted] in the caplacizumab group and [redacted] in the placebo group. During the overall treatment period, including the four-week follow-up, patients in the caplacizumab and placebo groups spent [redacted] and [redacted], respectively, in the ICU.

Likewise, the mean (SE) duration of hospital stays was shorter in the caplacizumab group [redacted] during the double-blind period and [redacted] during the overall study period, including the follow-up) versus the placebo group [redacted] during the double-blind period and [redacted] during the overall study period, including the follow-up).

No statistical comparisons were reported for the differences in number of days in ICU and hospital.

Harms (Safety)

During the overall study period of HERCULES, almost all patients reported adverse events: 97.2% in the caplacizumab group and 97.3% in the placebo group. The most common adverse events reported in the caplacizumab group were epistaxis, headache, gingival bleeding, urticaria, pyrexia, fatigue, nausea, and aTTP episodes. There were fewer serious adverse events with caplacizumab (28 patients; 39.4%) compared with placebo (39 patients; 53.4%) during the overall study period. aTTP episodes were the most commonly reported serious adverse event, and the incidence of aTTP episodes was higher in the placebo group (39.7%) than in the caplacizumab group (12.7%). Five patients (7.0%) treated with caplacizumab and nine patients (12.3%) treated with placebo withdrew from the study or treatment due to adverse events.

Bleeding events, hypersensitivity, and anti-drug antibody development were adverse events prespecified to be of interest for the CADTH review. The frequency of bleeding events was similar between treatment groups, occurring in 49 patients (69%) in the caplacizumab group and 49 patients (67.1%) in the placebo group. Likewise, the frequency of hypersensitivity reactions [redacted] and development of anti-drug antibodies (caplacizumab = 2.8%; placebo = 1.4%) were similar between groups during the overall study period.

Other Relevant Evidence

The TITAN study was considered a supportive study of the pivotal HERCULES RCT in the CADTH review of caplacizumab. TITAN was a phase II, multicenter, single-blinded, parallel design, placebo-controlled RCT conducted in adult patients who were symptomatic and experiencing acute episodes of aTTP that required treatment with PEX. Approximately 90% of patients in each group received concomitant corticosteroids. A total of 75 patients were included in the TITAN study; 36 received caplacizumab and 39 received placebo. The primary outcome in the TITAN study was confirmed platelet response. The mean duration of treatment with caplacizumab was approximately 38 days (with a maximum of 77 days).

Patients treated with caplacizumab reached a confirmed platelet response more rapidly than patients treated with placebo (hazard ratio of 2.20; 95% CI, 1.28 to 3.78; P = 0.005).

In terms of safety, almost every patient experienced at least one adverse event, and more than half of all patients experienced at least one serious adverse event. The most common adverse event was aTTP. Serious reports of aTTP and bleeding events were more common among patients treated with caplacizumab compared to placebo. [redacted]

[redacted], respectively, and bleeding events were reported by 54.3% and 37.8% of treated patients, respectively.

Although TITAN suggested that caplacizumab is more efficacious than placebo in patients receiving PEX and corticosteroids, the interpretation of the results is limited by concerns with the internal validity. More specifically, in terms of the single-blinded study design, the primary efficacy outcome, and lack of adjustment for multiplicity of statistical testing. As well, the generalizability of the results to the Canadian context may be limited given the lack of study sites in Canada, that not all patients received corticosteroids, and that the demographics of the study may not reflect the diversity of the patient population with aTTP in Canada.

Cost and Cost-Effectiveness

The submitted price of caplacizumab is $6,200 per 11 mg dose. Assuming 37.2 days of therapy (i.e., the mean exposure to caplacizumab for patients in the active treatment group of the HERCULES trial; the reported maximum was 65 days), the cost of caplacizumab for an aTTP episode is $236,840 per patient (maximum = $409,200).

The sponsor submitted a cost-utility analysis comparing caplacizumab in addition to standard of care to standard of care alone in adult patients with aTTP from the perspective of a Canadian public health care payer. Standard of care 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 therapies, such as rituximab. The analysis was conducted over a lifetime time horizon (60 years) with cycle length defined as three months. Patients entered the model in an acute aTTP state and, during the first cycle, patients could experience events with long-term consequences, such as a myocardial infarction (MI), stroke, or death. Patients could also experience other adverse events, such as a PEX complication, 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. Relative risks of these events in the caplacizumab group were derived from the HERCULES trial, while the underlying probability of each event occurring in the standard of care group was derived from a variety of sources. Following the first cycle, patients who remained alive transitioned to the remission phase in either a chronic MI or chronic stroke health state if they had MI or stroke, respectively, or to a no neurologic or cardiac condition health state. As the analysis only modelled 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 a disutility for an acute aTTP episode and an acute and chronic utility multiplier for MI or stroke events. Costs 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 specialist visits.

CADTH identified a number of limitations in the model submitted by the sponsor:

- The sponsor considered only a single episode of aTTP in its analysis, which is inconsistent with many patients’ lifetime experiences with aTTP recurrences.
- Not all deaths within the HERCULES trial for caplacizumab were accounted for in the economic model. The approach to model mortality during the acute aTTP episode further inflated the survival benefit of caplacizumab plus standard of care.
- aTTP relapses 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.
- The sponsor assumed the mortality rate of patients in remission was identical to the general population despite long-term observational studies reporting higher mortality. Overall mortality was underestimated.
- The health utility score of patients in remission without stroke or MI was likely overestimated 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 attempted to address most of these issues. The CADTH base-case analysis incorporated all deaths and recurrences in the caplacizumab group of the HERCULES trial to re-estimate relative risks; increased 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 to the HERCULES trial for certain relative risk parameters. In CADTH's base-case analysis, the incremental cost-effectiveness ratio associated with caplacizumab plus standard of care compared to standard of care alone was $237,053 per quality-adjusted life-year (QALY). At a willingness-to-pay of $50,000 per QALY, the price of caplacizumab would need to be reduced by approximately 75% to be considered cost-effective.

There is uncertainty associated with the cost-effectiveness of caplacizumab plus standard of care as CADTH was unable to consider future aTTP episodes, specifically the potential impact of caplacizumab on reducing or delaying them, or the costs associated with further treatment for acute episodes. In the HERCULES trial, the use of caplacizumab in addition to standard of care was associated with [redacted], which is a key driver in the economic analysis. 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 also key drivers of the cost-effectiveness results.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

February 19, 2020 Meeting (Initial)

Regrets

None

Conflicts of Interest

None

August 19, 2020 Meeting (Reconsideration)

Regrets

One CDEC member was absent.

Conflicts of Interest

None